



(51) International Patent Classification:

A61K 9/20 (2006.01) A61K 31/137 (2006.01)

(21) International Application Number:

PCT/EP2010/004459

(22) International Filing Date:

21 July 2010 (21.07.2010)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

09009499.6 22 July 2009 (22.07.2009) EP

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NL, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: HOT-MELT EXTRUDED CONTROLLED RELEASE DOSAGE FORM

(57) Abstract: The invention relates to a hot-melt extruded pharmaceutical dosage form with controlled release of a pharmacologically active ingredient (A) embedded in a matrix comprising a polymer (C), the dosage form exhibiting a breaking strength of at least 300 N and having an oblong shape comprising a longitudinal direction of extension, a transversal direction of extension orthogonal to the longitudinal direction of extension, a front side, an opposite back side and a circumferential rim between said front and back side; wherein the core of the pharmaceutical dosage form has a morphological orientation caused by hot-melt extrusion that is substantially orthogonal to the longitudinal direction of extension of the dosage form; and/or - the release per area of the pharmacologically active ingredient (A) through the front side and the opposite back side is faster than the release through the circumferential rim.



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**HOT-MELT EXTRUDED CONTROLLED RELEASE DOSAGE FORM**

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**FIELD OF THE INVENTION**

The invention relates to a hot-melt extruded pharmaceutical dosage form exhibiting an increased breaking strength (resistance to crushing). The pharmaceutical dosage form is characterized by a modified release profile of the pharmacologically active compound contained therein.

**BACKGROUND ART**

For many pharmaceutically active compounds it is preferred to have them orally administered by way of tablets. It is well known that depending on how a pharmaceutically active ingredient is formulated into a tablet its release pattern can be modified. In this regard, tablets providing a controlled release profile are of primary importance. With controlled release tablets care has to be taken that under no circumstances the pharmaceutically active ingredient will be released completely and instantaneously in an uncontrolled manner ("dose-dumping") since regularly the dosage used for controlled, particularly for retarded release tablets is much higher than for non-retarded release tablets. This may cause serious adverse effects or even death depending on the active ingredient and potency thereof.

Controlled release (e.g. retarded release, delayed release, prolonged release, sustained release, and the like) may be based upon various concepts such as coating the pharmaceutical dosage form with a controlled release membrane, embedding the pharmacologically active compound in a matrix, binding the pharmacologically active compound to an ion-exchange resin, forming a complex of the pharmacologically active compound, and the like. In this context it can be referred to, e.g., W.A. Ritschel, *Die Tablette*, 2. Auflage, Editio Cantor, Aulendorf, 2002.

Pharmaceutical dosage forms having an increased breaking strength (resistance to crushing) have been recently reported. Dosage forms of this type may also exhibit a certain degree of controlled release of the pharmacologically active compound contained therein. The major advantage of such pharmaceutical dosage forms is that comminuting, particularly pulveri-

zation, by conventional means, such as grinding in a mortar or fracturing by means of a hammer, is impossible or at least substantially impeded.

On the one hand, pharmaceutical dosage forms having an increased breaking strength are useful for avoiding drug abuse of the pharmacologically active compound contained therein. Many pharmaceutical active compounds, in addition to having excellent activity in their appropriate application, also have abuse potential, i.e., they can be used by an abuser to bring about effects other than those intended. Opiates, for example, which are highly active in combating severe to very severe pain, are frequently used by abusers to induce a state of narcosis or euphoria. In order to make abuse possible, the corresponding pharmaceutical dosage forms, such as tablets or capsules are comminuted, for example ground in a mortar, by the abuser, the active compound is extracted from the resultant powder using a preferably aqueous liquid and the resultant solution, optionally after being filtered through cotton wool or cellulose wadding, and is administered parenterally, in particular intravenously. An additional phenomenon of this kind of administration, in comparison with abusive oral administration, is a further accelerated increase in active compound levels giving the abuser the desired effect, namely the "kick" or "rush". This kick is also obtained if the powdered pharmaceutical dosage form is administered nasally, i.e. is sniffed. Since controlled-release pharmaceutical dosage forms containing active compounds with abuse potential do not give rise to the kick desired by the abuser when taken orally even in abusively high quantities, such pharmaceutical dosage forms are also comminuted and extracted in order to be abused. Pharmaceutical dosage forms exhibiting an increased breaking strength, however, may not be powdered by conventional means and thus, cannot be administered nasally thereby avoiding drug abuse. In the context of such tamper resistant dosage forms, it can be referred to, e.g., WO 2005/016313, WO 2005/016314, WO 2005/ 063214, WO 2005/102286, WO 2006/002883, WO 2006/002884, WO 2006/002886, and WO 2006/082097.

On the other hand, pharmaceutical dosage forms having an increased breaking strength are useful for avoiding an (unintentional) overdose of the pharmacologically active compound contained therein, which overdose would otherwise be caused by diminishing the retardant effect due to pulverization. It is known that many patients, particularly older patients frequently have difficulties in taking solid pharmaceutical dosage forms, such as tablets, gelatine capsules, etc. They choke on them and sometimes develop pronounced aversion to such pharmaceutical dosage forms. To counter this problem, various apparatuses have been developed by means of which conventional solid pharmaceutical dosage forms may be comminuted or pulverized ("tablet crushers"). Such apparatuses are used, for example, by the care staff in old people's homes. The pharmaceutical dosage forms are then adminis-

tered to the people being cared for not as tablets etc. but rather as powder, for example to get round the difficulties involved in swallowing tablets. However, the comminution of pharmaceutical dosage forms with such apparatuses is problematic if the pharmaceutical dosage forms are prolonged-release formulations. As a rule, comminution results in destruction of the inner structure of the pharmaceutical dosage form, which is responsible for the prolonged release, so doing away with the prolonged-release action. Consequently, after administration, frequently all the physiologically active substance originally contained in the pharmaceutical dosage form is released in a relatively short time, whereby a comparatively very high plasma concentration of the substance is abruptly reached within a relatively short time frame. In this way, the originally prolonged-release formulations become immediate release formulations. Depending on the physiological activity of the substance, this may cause considerable side-effects however, and in extreme cases may even lead to the death of the patient. Pharmaceutical dosage forms having an increased breaking strength, however, cannot be comminuted by tablet crushers and thus, have to be swallowed as a whole thereby avoiding any (unintentional) overdose. In this context, it can be further referred to, e.g., WO 2006/082099.

The release profile of controlled-release formulations depends on a variety of factors, such as properties of the pharmaceutical dosage form per se, nature and content of the matrix, nature of the release medium, nature and content of the active compound, nature and content of further pharmaceutical excipients as well as the interrelationship of these factors. When the control of the release profile relies on a polymer matrix in which the active compound is embedded, the release rate depends on the properties of the pharmaceutical dosage form as such, e.g. its geometry, method of manufacture, additives and excipients contained therein, and the like. Further, the release rate depends on the properties of the matrix polymer, such as molecular weight, viscosity, particle properties, interaction with other polymers, chain entanglements, degree of cross-linking, chemical nature of monomer units, interaction of the matrix material with the release medium (e.g., swelling and gelling), and the like. Still further, the release rate depends on the properties of the active compound, e.g., its dose, particle size, particle form and its solubility in the release medium, which in turn is a function of various properties, such as molecular size, molecular weight, ionogenicity, acidity, steric hindrance, arrangement of dipoles, hydrophilicity, etc. Furthermore, the release rate depends on the individual interactions of a given matrix material with a given active compound (cf. Ning Wu et al., *Journal of Controlled Release* 102 (2005) 569-81; V.S. Manthena et al., *Am J Drug Deliv.* 2004 2(1) 43-57).

The release profile of conventional pharmaceutical dosage forms that do not exhibit an increased breaking strength can usually be adjusted within certain limits, usually by the variation of the content and/or the nature of the pharmaceutical excipients, such as the matrix forming polymer.

In some cases it has also been reported that the release of a drug in the body can be controlled by the surface area to volume ratio of a conventional dosage form which does not exhibit an increased breaking strength. For example, US 5,427,798 discloses film coated tablets containing bupropion hydrochloride and having a surface area to tablet volume of 3:1 to 25:1  $\text{cm}^{-1}$  for tablets of 50, 100 and 150 mg drug content. Similarly, US 4,940,556 and US 5,198,226 disclose spheroids containing dihydropyridine calcium channel blockers and having area radius to circumference radius ratios in the range of 0.85 to 1.0.

With respect of pharmaceutical dosage forms exhibiting an increased breaking strength, however, the variation of the content, the nature of the pharmaceutical excipients and/or the surface area to volume ratio also affects the mechanical properties. This is because the increased breaking strength of the pharmaceutical dosage form typically relies on the presence of a particular polymer that is processed by a particular method when manufacturing the pharmaceutical dosage form. It seems that said polymer also serves as a matrix embedding the pharmacologically active compound. In consequence, the polymer matrix that is essential to the breaking strength of the pharmaceutical dosage form simultaneously serves as a controlled release matrix and thus, varying the content, nature and/or spatial distribution of the polymer causes both, a change of the release profile as well as a change of the mechanical properties of the pharmaceutical dosage form.

Particular problems arise when the dose of the pharmacologically active compound and thus, also the total weight of the pharmaceutical dosage form is comparatively high. Depending upon the content and the nature of the pharmacologically active compound and of the pharmaceutical excipients, the retardant effect of the polymer may be so strong that the pharmaceutical dosage form cannot be adapted to a specific dosing regimen, e.g., twice daily, particularly when the increased breaking strength is to be maintained.

On the one hand, a decrease of the content of the retardant polymer for the purpose of accelerating drug release would substantially affect the mechanical properties of the pharmaceutical dosage form and in a worst case scenario, would completely diminish its specific and unique mechanical properties (breaking strength). Further, a decrease of the content of the matrix polymer beyond a certain limit may cause a deterioration or even loss of

other desired properties, such as storage stability. A poor storage stability results, e.g., in a change of the release profile over time.

On the other hand, the addition of non-retardant pharmaceutical excipients (auxiliaries) for the purpose of weakening the retardant effect of the retardant polymer would increase the total weight of the dosage form. As highly dosed pharmaceutical dosage forms have comparatively high total weights anyway, a further increase of the total weight is disadvantageous and could deteriorate patient compliance (e.g. swallowability).

Furthermore, a pharmaceutical formulation or its mode of manufacture, e.g. for an oral dosage form, might undergo modifications during clinical testing, for example with respect to the ingredients used or to the relative amounts of the pharmaceutical excipients, or with respect to the reaction conditions and reactants used during manufacture. Frequently, such modifications at least to some extent have an impact on the release profile of pharmaceutically active ingredients. This is particularly unpleasant if for a specific formulation an approved optimized release profile has already been found which cannot be reproduced with the modified formulation. In such a case, the clinical tests have either to be interrupted or have to be started from the beginning. Given the huge expenditures necessary to bring a new drug formulation up to and through clinical testing the above scenario has indeed proven to be rather unsatisfactory.

Thus, there is a demand for tamper resistant pharmaceutical dosage forms the release profile of which may be varied within certain limits without diminishing the tamper resistance, without substantially changing the nature or amount of the pharmaceutical excipients, and without deteriorating the compliance of the pharmaceutical dosage form.

It is an object of the invention to provide pharmaceutical dosage forms having advantages compared to pharmaceutical dosage forms of the prior art.

This object has been solved by the subject-matter of the patent claims.

## SUMMARY OF THE INVENTION

The invention relates to a hot-melt extruded pharmaceutical dosage form with controlled release of a pharmacologically active ingredient embedded in a matrix comprising a polymer, the dosage form exhibiting a breaking strength of at least 300 N, preferably at least 500 N, and having an oblong shape comprising a longitudinal direction of extension, a transversal

direction of extension orthogonal to the longitudinal direction of extension, a front side, an opposite back side and a circumferential rim between said front and back side;

wherein

- the core of the pharmaceutical dosage form has a morphological orientation caused by hot-melt extrusion that is substantially orthogonal to the longitudinal direction of extension of the dosage form; and/or
- the release of the pharmacologically active ingredient through the front side and the opposite back side is faster than the release through the circumferential rim.

It has been surprisingly found that the release rate of the dosage form can be modified by modifying the shape of the extrudate from which the dosage form is formed, in particular by modifying the area ratio of the front faces (cut surfaces) of the extrudate relative to the jacket (barrel) of the extrudate.

Surprisingly, the release rate is accelerated when the area of the cut surfaces increases. It seems that said cut surfaces exhibit a faster release of the pharmacologically active ingredient than the jacket (barrel) of the extrudate. Thus, when press-forming a pharmaceutical dosage form from an extrudate, those surface areas of the pharmaceutical dosage form originating from the front faces of the extrudate seem to show a faster release than those surface areas originating from the jacket (barrel) of the extrudate. This effect can be advantageously used in order to adjust the release profile of the pharmacologically active ingredient from the pharmaceutical dosage form, either in an accelerating manner or in a decelerating manner.

Furthermore, it has been surprisingly found that the mechanical properties of the pharmaceutical dosage form, particularly its breaking strength, depend upon the relative position of the direction of extrusion within the body of the pharmaceutical dosage form. Thus, the mechanical properties of the pharmaceutical dosage forms can be improved by placing the direction of extrusion into a proper direction within the body of the dosage form.

## BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a schematic view of a preferred embodiment of the pharmaceutical dosage form according to the invention. Figure 1A is a side view and Figures B<sup>1</sup> to B<sup>3</sup> are top views of cross-sections of alternative dosage form having different oblong shape.

Figure 2 schematically illustrates the conventional manufacture of oblong hot-melt extruded pharmaceutical dosage forms having an increased breaking strength. Figure 2A shows the separation of the extrudate from the extruded strand having a circular cross-section, Figure 2B shows the shaping of the dosage form from the extrudate by means of a tableting tool equipped with upper punch and lower punch, and Figure 2C shows the resultant dosage form, Figure 2C<sup>1</sup> as a side view and Figure 2C<sup>2</sup> as top view of the cross-section.

Figure 3 schematically illustrates the inventive manufacture of oblong hot-melt extruded pharmaceutical dosage forms having an increased breaking strength. Figure 3A shows the separation of the extrudate from the extruded strand having an oblong cross-section, Figure 3B shows the shaping of the dosage form from the extrudate by means of a tableting tool equipped with upper punch and lower punch, and Figure 3C shows the resultant dosage form, Figure 3C<sup>1</sup> as a side view and Figure 3C<sup>2</sup> as top view of the cross-section.

Figure 4 schematically illustrates a preferred embodiment of the dosage form according to the invention, having two recesses on opposing sides. Figure 4A illustrates top view and side view also indicating the curvature of the circumference surrounding the recesses. Figure 4B illustrates top view and side view also indicating the direction of extrusion relative to the body of the dosage form.

Figure 5 shows the result of a three dimensional terahertz measurement. Figure 5A shows the results of a terahertz pulsed imaging measurement (image of the cross section of an extrusion strand). Figure 5B shows the results of a terahertz pulsed imaging measurement (image of the longitudinal section of an extrusion strand).

Figure 6 shows the dissolution profile of example 1 shaped to a 7\*17 mm oblong tablet.

Figure 7 shows the dissolution profile of example 1 shaped to a 7\*17 mm H9-shaped tablet.

Figure 8 shows the dissolution profile of example 2 shaped to a 9\*21 mm oblong tablet.

Figure 9 shows the dissolution profile of example 2 shaped to a 9\*21 mm H0-shaped tablet.

Figure 10 shows the dissolution profile of example 2 shaped to a 8.6\*22.6 mm H1-shaped tablet.



Figure 11 shows the dissolution for example 1: comparison of H9 format from round extrudate to oblong format from oblong extrudate.

Figure 12 shows the dissolution for example 2: comparison of H0 format from round extrudate to oblong format from oblong extrudate.

Figure 13 shows the dissolution for example 3: comparison of oblong crude extrudate to tablet from extrudate that has been folded twice before.

## DETAILED DESCRIPTION OF THE INVENTION

A first aspect of the invention relates to a hot-melt extruded pharmaceutical dosage form with controlled release of a pharmacologically active ingredient (A) embedded in a matrix comprising a polymer (C), the dosage form preferably being adapted for oral administration and having an oblong shape comprising a longitudinal direction of extension, a transversal direction of extension orthogonal to the longitudinal direction of extension, a front side, an opposite back side and a circumferential rim between said front and back side;

wherein

- the core of the pharmaceutical dosage form has a morphological orientation caused by hot-melt extrusion that is substantially orthogonal to the longitudinal direction of extension of the dosage form; and/or
- the release per area of the pharmacologically active ingredient (A) through the front side and the opposite back side is faster than the release through the circumferential rim.

A preferred embodiment of the hot-melt extruded pharmaceutical dosage form according to the invention is further schematically illustrated in Figure 1.

Figure 1A is a perspective view of a preferred embodiment of a pharmaceutical dosage form (1) comprising a front side (2a), a back side (2b) as well as a circumferential rim (3) between front side (2a) and back side (2b). Plane (4) lies within the body of the pharmaceutical dosage form (1) and includes longitudinal direction of extension (5) that is orthogonal to transversal direction of extension (6). This embodiment can be regarded as a biconvex oblong dosage form.

Figures 1B<sup>1</sup>, 1B<sup>2</sup> and 1B<sup>3</sup> are top views of alternative preferred embodiments of plane (4) including circumferential rim (3), longitudinal direction of extension (5) and transversal direction of extension (6). According to the embodiment depicted in Figure 1B<sup>1</sup>, circumferential rim (3) assumes the shape of an ellipse with longitudinal direction of extension (5) being the semi-major axis and transversal direction of extension (6) being the semi-minor axis. According to the embodiment depicted in Figure 1B<sup>2</sup>, circumferential rim (3) assumes the shape of two half-circles with a rectangle in between. According to the embodiment depicted in Figure 1B<sup>3</sup>, circumferential rim (3) assumes the shape of a rectangle with rounded corners.

When manufacturing conventional hot-melt extruded oblong pharmaceutical dosage forms, a mass comprising the pharmacologically active ingredient and further pharmaceutical excipients is hot-melt-extruded through a die. Conventionally, the die has a circular shape yielding an extrudate with a circular cross-section (cylinder). Extrusion causes the constituents in the mass to somewhat orientate in a one-dimensional fashion such that the resultant extrudate (extruded strand) has a morphological orientation in the direction of extrusion. The morphological orientation can be visualized by suitable analytical methods.

Said extrudate is then separated (singulated), typically cut into cylinders, usually in a plane substantially orthogonal to the direction of extrusion. Each cylinder has two opposing surfaces as well as a circumference (barrel/jacket). The opposing surfaces are produced in the course of separating (e.g., cutting) the extrudate into cylinders. The circumference is produced in the course of the extrusion process (barrel/jacket of the extruded strand). Subsequently, said cylinders are press-formed into oblong dosage forms, e.g., by means of a tableting machine. For geometrical reasons, the cylinders are typically placed into the tableting tool so that the longitudinal axis of the cylinder parallels the longitudinal direction of extension of the punch.

Press-forming the extrudates typically changes the outer shape of the dosage form. Thus, the shape of the dosage form typically differs from the shape of the extrudate, which can be regarded as an intermediate of the manufacturing process.

When manufacturing the pharmaceutical dosage forms according to the invention, hot-melt-extrusion is preferably performed through an oblong die yielding an extrudate with an oblong cross-section. Thus, separation (singulation) yields slices (extrudates) having two opposite oblong surfaces, e.g. cut surfaces. When placing said slices into a tableting tool comprising upper punch and lower punch in a manner so that the opposing surfaces of oblong shape

face said upper and lower punch, respectively, the front and opposite back side of the dosage form are made from (originate from) the cut surfaces of the slice, whereas in the circumferential rim of the dosage form is made from (originates from) the barrel/jacket of the extrudate. In consequence, the direction of extrusion is substantially orthogonal to the longitudinal direction of extension of the dosage form.

A skilled person is fully aware that when press-forming the dosage form from the extrudate, the morphological orientation of the material in the extrudate is changed. At least in the outer regions of the extrudate press-forming causes the material to flow in order to exactly fill the die/punch that is used in press-forming and that determines the final outer shape of the dosage form. However, the material forming the core of the extrudate is not moved or only moved to a slight extent in the course of press-forming and hence, the core substantially maintains its morphological orientation. Thus, the core of the dosage form serves as a reference point or bench mark to define the morphological orientation of the material relative to the outer dimensions of the dosage form.

For the purpose of the specification, the core of the dosage form constitutes the centre volume element having at most 50% of the total volume of the dosage form, more preferably at most 40%, still more preferably at most 30%, yet more preferably at most 20% and in particular at most 10% of the total volume of the dosage form. Therefore, when deciding whether the morphological orientation of the material in the core is substantially orthogonal to the direction of extrusion, the proper core element should be investigated by suitable analytical methods such as terahertz spectroscopy or high-resolution imaging techniques like electron microscopy, electron raster microscopy, electron force microscopy, NIR-microscopy and the like. Alternative methods include solid state NMR, photoelectron spectroscopy and X-ray methods.

The essential differences of the preparation of conventional oblong dosage forms and inventive oblong dosage forms by hot-melt extrusion are further schematically illustrated in Figures 2 and 3.

Figure 2 schematically illustrates the conventional manufacture of oblong hot-melt extruded pharmaceutical dosage forms having an increased breaking strength.

Figure 2A shows the extruded strand (7) as well as cylindrical extrudate (8) that has been separated, e.g. cut, to the desired length and weight. The direction of extrusion is indicated by the horizontal lines (9) at the jacket (barrel) of cylindrical extrudate (8) as well as by the

spots (10) at the front surfaces. Each spot (10) stands for the end of a horizontal line (9). Horizontal lines (9) as well as spots (10) are indicated for illustration purposes only, as a marker of the direction of extrusion, which can be detected by suitable methods. In reality, however, there are neither horizontal lines (9) nor spots (10). Extruded strand (7) and extrudate (8) have a circular or oblong cross-section, i.e., hot-melt extrusion has been performed through a circular or oblong die.

Figure 2B shows extrudate (8) in the tableting tool that is equipped with upper punch (11a) and lower punch (11b). Extrudate (8) is placed into the tableting tool such that the jacket (barrel) of the extrudate faces upper punch (11a) as well as lower punch (11b). The front surfaces of the extrudate with spots (10), however, do not face any of the punches.

Figure 2C shows the resultant conventional tablet (1), Figure 2C<sup>1</sup> as a side view and Figure 2C<sup>2</sup> as top view of the cross-section. Plane (4) lies within the body of the pharmaceutical dosage form (1) and includes longitudinal direction of extension (5). The core (12) of the dosage form has a morphological orientation caused by hot-melt extrusion (indicated by horizontal lines (9)) that is substantially parallel to the longitudinal direction of extension (5)

In contrast to Figure 2 (comparative), Figure 3 schematically illustrates the manufacture of hot-melt extruded pharmaceutical dosage forms according to the invention.

Figure 3A shows the extruded strand (7) as well as oblong-cylindrical extrudate (8) that has been separated, e.g. cut, to the desired length and weight. The direction of extrusion is indicated by the horizontal lines (9) at the jacket (barrel) of cylindrical extrudate (8) as well as by the spots (10) at the front surfaces. Each spot (10) stands for the end of a horizontal line (9). Horizontal lines (9) as well as spots (10) are indicated for illustration purposes only, as a marker of the direction of extrusion, which can be detected by suitable methods. In reality, however, there are neither horizontal lines (9) nor spots (10). Extruded strand (7) and extrudate (8) have an oblong cross-section, i.e., hot-melt extrusion has been performed through an oblong die.

Figure 3B shows extrudate (8) in the tableting tool that is equipped with upper punch (11a) and lower punch (11b). Extrudate (8) is placed into the tableting tool such that the front surfaces of the extrudate of oblong shape with spots (10) face upper punch (11a) as well as lower punch (11b). The jacket (barrel) of the extrudate with horizontal lines (9), however, does not face any of the punches.

Figure 3C shows the resultant tablet (1) according to the invention, Figure 3C<sup>1</sup> as a side view and Figure 3C<sup>2</sup> as top view of the cross-section. Plane (4) lies within the body of the pharmaceutical dosage form (1) and includes longitudinal direction of extension (5). The core (12) of the dosage form has a morphological orientation caused by hot-melt extrusion (indicated by spots (10)) that is substantially orthogonal (perpendicular) to the longitudinal direction of extension (5).

The advantages of the invention become particularly evident when manufacturing H-shaped tablets. H-shaped tablets are formed by means of an H-plunger (H-punch) and are schematically illustrated in Figure 4. Compared to conventional dosage forms such as biconvex tablets, H-shaped tablets show a different breaking behavior in the breaking strength test.

Further, compared to round tablets, a difference in the orientation of the extrudate could also contribute to the advantages of the dosage form according to the invention. During the tableting of a round shape the compression force is typically applied by the punches on the cross-section of the extrudate strand, i.e. on its cut surface. During the tableting of the oblong shape compression force is typically applied rectangular to the cross-section of the extrudate strand, i.e. on its jacket or barrel.

The pharmaceutical dosage form according to the invention is hot-melt extruded.

Hot-melt extruded dosage forms are complex mixtures of active ingredients, functional excipients, and processing aids. Hot-melt extrusion offers several advantages over traditional pharmaceutical processing techniques including the absence of solvents, few processing steps, continuous operation, and the possibility of the formation of solid dispersions and improved bioavailability (cf. MM Crowley et al., *Drug Dev Ind Pharm* 2007, 33(9), 909-26; and MA Repka et al., *ibid*, 33(10), 1043-57).

Hot melt-extruded dosage forms can be distinguished from conventional dosage forms, e.g. from other thermoformed dosage forms, due to the morphological orientation caused by the extrusion process. Without intending on being bound to any scientific theory, it is believed that the one-dimensional processing of the hot-melt mass in direction of the extrusion die and the final squeezing therethrough causes morphological orientation processes on molecular and supramolecular level, respectively, that still can be detected in the final dosage form, i.e. even after the extrudate has been further shaped to yield the final dosage form.

Details and preferred embodiments of hot-melt extrusion are described in connection with the methods for preparing the pharmaceutical dosage form according to the invention.

The pharmaceutical dosage form according to the invention has an oblong shape.

For the purpose of the specification, the term "oblong" preferably refers to any three-dimensional body that is longer than high and wide, respectively. The pharmaceutical dosage form according to the invention comprises a longitudinal direction of extension and a transversal direction of extension orthogonal to the longitudinal direction of extension.

The pharmaceutical dosage form according to the invention comprises a cross-sectional area, preferably the main area of extension of the dosage form, including the longitudinal direction of extension as well as the transversal direction of extension, which are orthogonal (perpendicular) to one another.

The main area of extension is preferably the largest cross-sectional area of the pharmaceutical dosage form.

The longitudinal direction of extension is preferably the maximum extension of the dosage form, preferably the maximum end-to-end distance within the main area of extension of the dosage form.

The transversal direction of extension is preferably the maximum extension of the dosage form orthogonal (perpendicular) to the longitudinal direction of extension, preferably within the main area of extension of the dosage form.

The oblong shape of the dosage form can also be expressed in terms of the relative length ratio of the longitudinal direction of extension to the transversal direction of extension. Typically, the longitudinal direction of extension is longer than the transversal direction of extension.

Preferably, the relative length ratio of the longitudinal direction of extension to the transversal direction of extension is at least 1.1 : 1, at least 1.2 : 1, at least 1.3 : 1, at least 1.4 : 1 or at least 1.5 : 1; more preferably at least 1.6 : 1, at least 1.7 : 1, at least 1.8 : 1, at least 1.9 : 1 or at least 2.0 : 1; still more preferably at least 2.1 : 1, at least 2.2 : 1, at least 2.3 : 1, at least 2.4 : 1 or at least 2.5 : 1; yet more preferably at least 2.6 : 1, most preferably at least 2.7 : 1 and in particular at least 2.8 : 1. In a particularly preferred embodiment, the relative length

ratio of the longitudinal direction of extension to the transversal direction of extension is  $2.6 \pm 0.2 : 1$ ,  $2.8 \pm 0.2 : 1$  or  $3.0 \pm 0.2 : 1$ .

Preferably, the pharmaceutical dosage form according to the invention comprises a monolithic core. In this regard, monolithic is to be understood as formed or composed of material without joints or seams and constituting a massive undifferentiated and rigid whole. When the dosage form does not comprise a coating, the entire dosage form is preferably monolithic. When the dosage form is film-coated, preferably only the core is monolithic.

The pharmaceutical dosage form according to the invention comprises a front side, an opposite back side and a circumferential rim between said front and back side.

Typically, the pharmaceutical dosage form according to the invention assumes the form of a tablet. The pharmaceutical dosage form is preferably not in film form.

The pharmaceutical dosage form according to the invention may assume various shapes. From top view, the shape of the pharmaceutical dosage form can be any oblong shape such as substantially elliptic, rectangular and the like. Preferably, from side view, the shape of the pharmaceutical dosage form can be substantially flat-convex, biconvex, flat with facet, flat without facet, cyclic, and the like.

In a particularly preferred embodiment, the pharmaceutical dosage form according to the invention can be described as a body having a recess or cavity on at least one side, preferably two recesses or two cavities on two sides, preferably on opposing sides. Alternatively, said cavities and recesses, respectively, may be regarded as bulges, indentations, troughs, hollows, depressions, synclines, deepenings, and the like.

Figure 4 schematically illustrates a preferred embodiment of such dosage form according to the invention, having two recesses (13) on opposing sides. Figure 4A illustrates top view and side view also indicating the curvature of the circumference (14) surrounding the recesses (13). Figure 4B illustrates top view and side view also indicating the direction of extrusion relative to the body of the dosage form, i.e. horizontal lines (9) as well as spots (10).

As the cross-sectional area of the dosage form depicted in Figure 4 assumes the shape of an H, for the purpose of the specification this shape of dosage form or tablet is also denoted as "H-shaped". For distinguishing purposes, preferred conventional oblong dosage forms are referred to as being "biconvex".

The general shape of the dosage form that are at least related or similar to that one depicted in Figure 4 can also be described as comprising a longitudinal axis and two opposite longitudinal edges, a transversal axis perpendicular to the longitudinal axis and two opposite transversal edges, a front side, an opposite back side and a circumferential rim between said front and back side, wherein the front side and/or the back side comprise a basis area and wherein the front side and/or the back side comprise at least one bulge which extends above said basis area, said at least one bulge being present at and/or adjacent to at least a section of one or both longitudinal edges and/or at and/or adjacent to at least a section of one or both transversal edges and/or between both longitudinal edges and both transversal edges. The front side and/or the back side of the dosage form, in particular the basis area of the front side and/or the basis area of the back side, can further comprise at least one indentation.

Since the dosage form of the invention has a longitudinal axis being substantially longer than its transversal axis, it exhibits an oblong shape. The longitudinal axis is typically extending through the middle part of the dosage form between both opposing longitudinal edges from one transversal edge to the opposite transversal edge, in particular in such a way that its length is maximized. The transversal axis is typically extending from one longitudinal edge to the opposite longitudinal edge, in particular in such a way that its length is maximized. The transversal axis is oriented perpendicular to the longitudinal axis.

The basis area of the front side and/or the back side of the dosage form of the invention does not necessarily have to be flat, but can in one embodiment exhibit an irregular or regular three dimensional pattern, which, however, is not extending to any significant degree towards the dimension of a bulge or an indentation.

The average distance between the front basis area and the back basis area of one embodiment of the dosage form of the invention usually is smaller than the length of its transversal axis. Those opposite sides of the dosage form which have the smallest average distance usually comprise the front and the back basis areas.

According to another preferred embodiment, a dosage form is provided, wherein the front side and the back side each comprise at least one bulge at least along a section at and/or adjacent to both longitudinal edges and/or at least along a section at and/or adjacent to both transversal edges. In this respect it is even more preferred in certain cases that said front side and said back side comprise an at least essentially continuous bulge at and/or adjacent



to at least two third of both opposite longitudinal edges and/or at and/or adjacent to at least two third of both opposite transversal edges.

The bulge may have any geometric cross-section, and can, for example, be rounded or can have a rectangular, triangular or square cross-section. The bulges preferably have a width which is less than half the width, more preferably less than one third of the width of the dosage form. The length of the bulges can vary to a great extent. It is preferred that the overall length of an individual bulge is at least one half of the length of the longitudinal edge or of the transversal edge, depending on its location. Typically, the overall length of a bulge is much longer than its width, e.g. several times the width of the bulge, such as more than 2, 3, 4, 5 or 6 times of its width, in particular when oriented in the longitudinal direction, or more than 2, 3 or 4 times of its width, in particular when oriented in the transversal direction. A bulge in the meaning of the present invention shall also comprise a series of adjacent bulge portions. These bulge portions, when viewed from above, can, for example, have the circumferential form of a circle, an oval, a rectangle, a square, a triangle or any other polygonal form, or may come close to these forms, or may even have an irregular form.

A bulge which is located at a longitudinal and/or at a transversal edge regularly passes over from the circumferential rim of the dosage form without a significant transition zone or transition step, i.e. without a "land". In such an embodiment there is a smooth transition from the rim part to the bulge part so that the outer surfaces of the rim and the bulge form a continuous surface at least over a section. A bulge which is positioned adjacent to a longitudinal or adjacent to a transversal edge is in contrast thereto not directly placed at the circumferential rim of the dosage form but is separated from the rim in the plane of the basis area by a portion, in particular a minor portion, which can be attributed to be part of the basis area. Said minor portion is known in the field of dosage form technology as "the land". This minor area usually has a width being smaller than the average width of the bulge itself. In a preferred embodiment, the land is in the range from about 0.05 mm to about 0.5 mm, e.g. about 0.1 mm.

In a particularly suitable embodiment, the dosage form of the invention is provided with bulges at both longitudinal edges and/or both transversal edges of both the front side and the back side of the dosage form, wherein these bulges extend at least over one half, more preferably over two thirds of the length of the longitudinal and/or transversal edges, even more preferably over the whole length of the longitudinal and/or transversal edges. In another preferred embodiment, the bulges continuously circumscribe the basis area of the front side and/or the back side, preferably the front and the back side, at and/or adjacent to

the respective longitudinal and transversal edges. Most desirable results in terms of an improved release profile can for example be obtained with dosage forms of the invention having bulges at both longitudinal edges of both sides of the dosage form. The cross-section of these dosage forms can be described to have or come close to an H-shape. By use of the expression "H-shaped" it shall just be indicated that a dosage form body having opposite, in particular rather flat, basis areas is provided with opposing bulges at the longitudinal edges on both sides of the dosage form body. For example, in one H-shape embodiment the bulges can protrude above their respective basis areas only to a minor extent compared to the lateral distance between the bulges along opposite longitudinal edges, e.g. up to about 1 or 2 mm.

In one preferred embodiment, a dosage form of the invention comprises at or adjacent to, in particular adjacent to, major portions of both opposite longitudinal edges, in particular at least along two thirds of the longitudinal edges, of the front side at least one bulge. In another preferred embodiment, a dosage form of the invention comprises at least one bulge at or adjacent to, in particular adjacent to, major portions of both opposite longitudinal edges, in particular at least along two thirds of the longitudinal edges, of both the front side and the back side of the dosage form. In another preferred embodiment, the dosage form of the invention comprises a circumferential bulge at or adjacent to, in particular adjacent to, the circumferential edge of the front side of said dosage form. In another preferred embodiment, the dosage form of the invention comprises a circumferential bulge at or adjacent to, in particular adjacent to, the circumferential edge of both the front side and the back side of said dosage form.

According to another suitable embodiment of the dosage form of the invention, it is provided that one or both longitudinal edges are essentially straight over at least a major part of their length and/or wherein one or both transversal edges are curved over a major part of their length, in particular curved in the form of an essentially circular arc. It is of course also possible that the longitudinal edges exhibit any other irregular or regular shape, for example, having a wave-like edge portion at least over a section. It is also possible that the transversal edge exhibits the shape of a triangle or any other polygonal shape. In general, both longitudinal and transversal edges form the circumference of the front side and the back side of the dosage form.

For most applications it is sufficient that the longitudinal length, that is, the length of the longitudinal axis, of the dosage form does not exceed 30 mm.

According to another embodiment, the dosage form of the invention preferably has an average thickness over the basis areas of the front and the back side of at least about 1 mm, and in particular of no more than about 9 mm, more in particular ranging from about 1 mm to about 7 mm or more in particular ranging from about 2 mm to about 6 mm.

According to one embodiment of the dosage form of the invention, the bulge extends perpendicular from the basis area of the front side and/or from the basis area of the back side in average from about 0.5 mm to about 2 mm, in particular from about 0.5 mm to about 1 mm.

Dosage forms of the invention preferably have a length in the longitudinal direction in the range of about 5 mm to about 30 mm, in particular in the range of about 15 mm to about 25 mm, more in particular about 17 mm to about 23 mm, even more in particular about 21 mm; a width in the range of about 5 mm to about 15 mm, in particular in the range of about 7 mm to about 12 mm, more in particular about 7 mm to about 10 mm, even more in particular 7 mm, 9 mm or 10 mm; and a thickness over the basis areas in the range of about 1 mm to about 6 mm, in particular in the range of about 1.5 mm to about 4 mm, even more in particular from 2 mm to about 4 mm, even further in particular from about 2.5 mm to about 3.5 mm.

As indicated above, the front side and/or the back side of the dosage form of the invention, in particular the basis area of the front side and/or the basis area of the back side, can in one embodiment further comprise at least one indentation. As has been found, this generally allows for a further improvement of the control of the release profile. The indentation in general in one embodiment represents a hollow space which is provided or embedded in the overall surface of the dosage form. For example, the front side, the back side, in particular the basis areas of the front side and/or the back side, the rim and/or at least one bulge can be provided with at least one indentation.

Indentations, when viewed from above, can have any irregular or regular shape, for example, the form of a square, rectangle, triangle, oval or circle. In one embodiment the indentations can take the form of a cylinder, a cube, a cuboid or a half-sphere, that is the walls and the opening forming the indentation come close to describing the form of a cylinder, a cube, a cuboid or a half-sphere. When viewed from above, the silhouette shape of the indentations has essentially the same width and length dimensions. It is also possible that when viewed from above, the silhouette shape of an indentation has a longer length dimension than a width dimension, for example, a length dimension which is at least 2, 3 or 4 times the width dimension. Accordingly, when viewed from above, the silhouette shape can be rather

elongate, e.g. a rectangle, and can have a regular silhouette form, e.g. straight, wave-like, or zig-zag, or can be rather irregular. In another embodiment an array of indentations can be formed, for example on the front side and/or the back side. For many applications it has been found to be sufficient that when viewed from above, the silhouette-shape of the indentation has a length dimension which is essentially identical to its width dimension as, for example, can be found with a circular, square-like or slightly oval or slightly rectangular shape. Said width dimension of the indentations, which is regularly determined parallel to the transversal axis, usually is less than one half of the transversal length of the dosage form, in particular less than one third of the transversal length of the dosage form. In one embodiment the width dimension is essentially identical to the depth of the indentation or is no more than 2 or 3 times the depth of the indentation. The length dimension of the indentation, which is regularly determined parallel to the longitudinal axis, usually is no longer than three quarters of the longitudinal length of the dosage form, in particular no longer than one half of the longitudinal length of the dosage form, and preferably no longer than one third of the longitudinal length of the dosage form. A hole in a dosage form is not an indentation in the meaning of the present invention. The silhouette shape and the depth of said indentations can vary depending on the desired release profile. Usually care should be taken that the depths of these indentations does not come too close to the thickness of the dosage form in order to prevent that upon handling a hole through the dosage form will be formed. Preferably the indentations have a depth which does not go beyond half the thickness of the dosage forms of the invention. For most applications it is frequently already sufficient that the maximum depth of said indentations does not go beyond one third of the thickness of the dosage form of the invention. The average thickness of the dosage form of the invention in general is determined as the distance between the front and back side of the dosage form or preferably between the basis area of the front side and the basis area of the back side.

By using the expressions front side and back side it shall be indicated that the dosage form of the invention has two opposite sides which each can be provided with bulges and/or indentations. In consequence, the selection of which is the front side and which is the back side is rather arbitrary. Accordingly, the expressions front side and back side could also be replaced by first side and opposite second side, respectively.

In one embodiment of the invention, there is provided a dosage form wherein the front side and/or the back side, in particular the, in particular essentially flat, basis area of the front side and/or the, in particular essentially flat, basis area of the back side, comprise in addition to at least one bulge at least one indentation, in particular between opposite longitudinal and/or transversal bulges.

In one embodiment of the invention it is provided that both the front and the back side comprise at least one indentation.

The indentations on the front side and on the back side of the dosage form of the invention can at least once be at least partially off-set or can at least once be positioned in a congruent manner. In one preferred embodiment, all the indentations of the front side and all indentations on the back side are at least partially off-set or are positioned in a congruent manner.

The indentations are regularly positioned in the base area of the front and/or the back side of the dosage form of the invention. It is for example possible to place two or more of such indentations adjacent to each other, e.g. in a row located between the longitudinal edges of the front and/or the back side. The indentations are preferably located between opposite longitudinally extending bulges at or adjacent to the longitudinal edges of the front and/or the back side of the dosage form of the invention.

In one preferred embodiment, a dosage form of the invention, in particular its oblong form, comprises at or adjacent to, in particular adjacent to, major portions of both longitudinal edges, in particular at least along two thirds of the longitudinal edges of the front side at least one bulge, and, in particular between the bulges along opposite longitudinal edges, at least one indentation.

In another preferred embodiment, a dosage form of the invention, in particular its oblong form, comprises at least one bulge at or adjacent to, in particular adjacent to, major portions of both opposite longitudinal edges, in particular at least along two thirds of the longitudinal edges of both the front side and the back side of the dosage form as well as at least one indentation on the front side and/or the back side, in particular on the basis area of the front side and/or the basis of the back side, of the dosage form, in particular between the bulges which are located along opposite longitudinal edges on the front side and/or the back side, respectively. In another preferred embodiment, the dosage form of the invention, in particular its oblong form, comprises a circumferential bulge at or adjacent to, in particular adjacent to, the circumferential edge of the front side and/or back side of said dosage form, and at least one indentation on the front side and/or back side, in particular on the basis area circumscribed by the circumferential bulge on the front and/or on the back side. In another preferred embodiment, the dosage form of the invention, in particular its oblong form, comprises a circumferential bulge at or adjacent to, in particular adjacent to, the

circumferential edge of both the front side and the back side of said dosage form and at least one indentation on the front side and the back side, in particular on the basis area circumscribed by the circumferential bulge of the front side and on the basis area circumscribed by the circumferential bulge of the back side.

In the Cartesian space, the principal dimensions of the pharmaceutical dosage form schematically illustrated in Figure 4 can be defined as a, b and c, where  $a = a_1 + a_2 + a_3$ ,  $b = b_1 + b_2 + b_3$  and  $c = c_1 + c_2 + c_3$ . Preferred relative dimensions D1 to D6 of the pharmaceutical dosage form depicted in Figure 4 can be defined in relative relations of a, b and c;  $a_1$ ,  $a_2$  and  $a_3$ ;  $b_1$ ,  $b_2$  and  $b_3$ ; and  $c_1$ ,  $c_2$  and  $c_3$ , respectively:

D1:  $c > a \geq b$ ;  $c > a > b$ ;

D2:  $c > 1.5 a$ ;  $c > 2 a$ ;  $c > 2.5 a$ ;  $c > 3 a$ ;

D3:  $a_2 > a_1 \cong a_3$ ;  $a_2 > 1.1 a_1 \cong 1.1 a_3$ ;  $a_2 > 1.2 a_1 \cong 1.2 a_3$ ;  $a_2 > 1.3 a_1 \cong 1.3 a_3$ ;

D4:  $b_2 \geq b_1 \cong b_3$ ;  $b_2 \geq 1.1 b_1 \cong 1.1 b_3$ ;  $b_2 \geq 1.2 b_1 \cong 1.2 b_3$ ;  $b_2 \geq 1.3 b_1 \cong 1.3 b_3$ ;

D5:  $b_2 \leq b_1 \cong b_3$ ;  $b_2 \leq 0.9 b_1 \cong 0.9 b_3$ ;  $b_2 \leq 0.8 b_1 \cong 0.8 b_3$ ;  $b_2 \leq 0.7 b_1 \cong 0.7 b_3$ ; and/or

D6:  $c_2 > c_1 \cong c_3$ ;  $c_2 > 1.1 c_1 \cong 1.1 c_3$ ;  $c_2 > 1.2 c_1 \cong 1.2 c_3$ ;  $c_2 > 1.3 c_1 \cong 1.3 c_3$ .

Preferred embodiments D7 to D18 regarding the absolute dimensions of the pharmaceutical dosage form depicted in Figure 4 are displayed in the table here below:

[mm]		D7	D8	D9	D10	D11	D12
a		$8.6 \pm 4.3$	$8.6 \pm 2.1$	$8.6 \pm 1.0$	$9.0 \pm 4.5$	$9.0 \pm 2.2$	$9.0 \pm 1.1$
b		$4.9 \pm 2.5$	$4.9 \pm 1.3$	$4.9 \pm 0.7$	$4.3 \pm 2.1$	$4.3 \pm 1.0$	$4.3 \pm 0.6$
c		$21.9 \pm 11.0$	$21.9 \pm 5.5$	$21.9 \pm 2.7$	$20.4 \pm 10.2$	$20.4 \pm 5.1$	$20.4 \pm 2.5$
[mm]		D13	D14	D15	D16	D17	D18
a		$9.0 \pm 4.3$	$9.0 \pm 2.1$	$9.0 \pm 1.0$	$9.1 \pm 4.5$	$9.1 \pm 2.2$	$9.1 \pm 1.1$
b		$4.1 \pm 2.5$	$4.1 \pm 1.3$	$4.1 \pm 0.7$	$4.5 \pm 2.1$	$4.5 \pm 1.0$	$4.5 \pm 0.6$
c		$20.5 \pm 11.0$	$20.5 \pm 5.5$	$20.5 \pm 2.7$	$20.5 \pm 10.2$	$20.5 \pm 5.1$	$20.5 \pm 2.5$

Preferred embodiments D19 to D30 regarding the absolute dimensions of the pharmaceutical dosage form depicted in Figure 4 are displayed in the table here below:

[mm]		D19	D20	D21	D22	D23	D24
a		$8.6 \pm 4.3$	$8.6 \pm 2.1$	$8.6 \pm 1.0$	$9.0 \pm 4.5$	$9.0 \pm 2.2$	$9.0 \pm 1.1$
	$a_1$	$3.3 \pm 1.6$	$3.3 \pm 0.8$	$3.3 \pm 0.4$	$3.5 \pm 1.8$	$3.5 \pm 0.9$	$3.5 \pm 0.5$
	$a_2$	$2.1 \pm 1.0$	$2.1 \pm 0.5$	$2.1 \pm 0.3$	$2.1 \pm 1.1$	$2.1 \pm 0.6$	$2.1 \pm 0.3$
	$a_3$	$3.3 \pm 1.6$	$3.3 \pm 0.8$	$3.3 \pm 0.4$	$3.5 \pm 1.8$	$3.5 \pm 0.9$	$3.5 \pm 0.5$
b		$4.9 \pm 2.5$	$4.9 \pm 1.3$	$4.9 \pm 0.7$	$4.3 \pm 2.1$	$4.3 \pm 1.0$	$4.3 \pm 0.6$
	$b_1$	$0.9 \pm 0.5$	$0.9 \pm 0.3$	$0.9 \pm 0.2$	$0.9 \pm 0.4$	$0.9 \pm 0.2$	$0.9 \pm 0.1$
	$b_2$	$3.1 \pm 1.5$	$3.1 \pm 0.7$	$3.1 \pm 0.4$	$2.6 \pm 1.3$	$2.6 \pm 0.6$	$2.6 \pm 0.3$

	b <sub>3</sub>	0.9 ± 0.5	0.9 ± 0.3	0.9 ± 0.2	0.9 ± 0.4	0.9 ± 0.2	0.9 ± 0.1
c		21.9 ± 11.0	21.9 ± 5.5	21.9 ± 2.7	20.4 ± 10.2	20.4 ± 5.1	20.4 ± 2.5
	c <sub>1</sub>	3.2 ± 1.6	3.2 ± 0.8	3.2 ± 0.4	3.3 ± 1.7	3.3 ± 0.9	3.3 ± 0.4
	c <sub>2</sub>	15.6 ± 7.8	15.6 ± 3.9	15.6 ± 2.0	13.8 ± 6.9	13.8 ± 3.5	13.8 ± 1.7
	c <sub>3</sub>	3.2 ± 1.6	3.2 ± 0.8	3.2 ± 0.4	3.3 ± 1.7	3.3 ± 0.9	3.3 ± 0.4
		D25	D26	D27	D28	D29	D30
a		9.0 ± 4.3	9.0 ± 2.1	9.0 ± 1.0	9.1 ± 4.5	9.1 ± 2.2	9.1 ± 1.1
	a <sub>1</sub>	3.2 ± 1.6	3.2 ± 0.8	3.2 ± 0.4	3.2 ± 1.8	3.2 ± 0.9	3.2 ± 0.5
	a <sub>2</sub>	2.6 ± 1.0	2.6 ± 0.5	2.6 ± 0.3	2.7 ± 1.1	2.7 ± 0.6	2.7 ± 0.3
	a <sub>3</sub>	3.2 ± 1.6	3.2 ± 0.8	3.2 ± 0.4	3.2 ± 1.8	3.2 ± 0.9	3.2 ± 0.5
b		4.1 ± 2.5	4.1 ± 1.3	4.1 ± 0.7	4.5 ± 2.1	4.5 ± 1.0	4.5 ± 0.6
	b <sub>1</sub>	1.0 ± 0.5	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.4	1.0 ± 0.2	1.0 ± 0.1
	b <sub>2</sub>	2.1 ± 1.5	2.1 ± 0.7	2.1 ± 0.4	2.5 ± 1.3	2.5 ± 0.6	2.5 ± 0.3
	b <sub>3</sub>	1.0 ± 0.5	1.0 ± 0.3	1.0 ± 0.2	1.0 ± 0.4	1.0 ± 0.2	1.0 ± 0.1
c		20.5 ± 11.0	20.5 ± 5.5	20.5 ± 2.7	20.5 ± 10.2	20.5 ± 5.1	20.5 ± 2.5
	c <sub>1</sub>	3.3 ± 1.6	3.3 ± 0.8	3.3 ± 0.4	3.3 ± 1.7	3.3 ± 0.9	3.3 ± 0.4
	c <sub>2</sub>	13.9 ± 7.8	13.9 ± 3.9	13.9 ± 2.0	13.9 ± 6.9	13.9 ± 3.5	13.9 ± 1.7
	c <sub>3</sub>	3.3 ± 1.6	3.3 ± 0.8	3.3 ± 0.4	3.3 ± 1.7	3.3 ± 0.9	3.3 ± 0.4

The pharmaceutical dosage form is preferably adapted for oral administration, i.e., should be capable of being swallowed. Thus, obscure geometrical forms which are obviously harmful cannot be regarded as pharmaceutical dosage forms according to the invention.

According to a preferred embodiment, the pharmaceutical dosage form is characterized by a specific aspect ratio. For the purpose of the specification, the aspect ratio is defined as the ratio of the main direction of extension of the dosage form to the maximum extension of the pharmaceutical dosage form orthogonal to said main direction of extension, e.g. maximum length to maximum height (and maximum length to maximum width, respectively).

Preferably, said aspect ratio is within the range of  $2.4 \pm 1.3 : 1$ , more preferably  $2.4 \pm 1.0 : 1$ , still more preferably  $2.4 \pm 0.8 : 1$ , yet more preferably  $2.4 \pm 0.6 : 1$ , most preferably  $2.4 \pm 0.4 : 1$  and in particular  $2.4 \pm 0.2 : 1$ .

According to a preferred embodiment, the pharmaceutical dosage form is characterized by a specific length to height to width ratio, where  $\text{length} > \text{height} \geq \text{width}$ . For the purpose of the specification, in this embodiment the length corresponds to the longitudinal direction of extension of the dosage form, the height corresponds to the maximum extension of the pharmaceutical dosage form orthogonal to the length, and the width corresponds to the transversal direction of extension orthogonal to the length and orthogonal to the width (Cartesian space). Preferably, the length to height to width ratio is within the range of  $4.7 \pm 2.0 : 2.0 \pm 1.0 : 1$ , more preferably  $4.7 \pm 1.6 : 2.0 \pm 0.8 : 1$ , still more preferably  $4.7 \pm 1.2 : 2.0 \pm 0.6 : 1$ ,

yet more preferably  $4.7 \pm 0.8 : 2.0 \pm 0.4 : 1$ , most preferably  $4.7 \pm 0.6 : 2.0 \pm 0.3 : 1$ , and in particular  $4.7 \pm 0.4 : 2.0 \pm 0.2 : 1$ .

Preferably, a portion of the surface of the pharmaceutical dosage form is convex, i.e. curved out or bulged outward, and another portion of its surface is concave, i.e. curved in or hollowed inward. For the purpose of the specification, the radius of curvature is not critical.

Preferably, the overall surface of the pharmaceutical dosage form can be divided into concave portions, convex portions and planar portions. Typically, the sum of the concave portions, convex portions and planar portions corresponds to the overall surface of the dosage form. However, at least theoretically, a given portion can be convex and concave simultaneously (saddle). Under these circumstances, the sum of the concave portions, convex portions and planar portions exceeds the overall surface of the dosage form.

In a preferred embodiment, the convex portion of the surface of the dosage form is at most 95%, more preferably at most 90% or at most 85%, still more preferably at most 80% or at most 75%, yet more preferably at most 70% or at most 65%, most preferably at most 60% or at most 55% and in particular at most 50% or at most 45%, based on the sum of concave portions, convex portions and planar portions.

In another preferred embodiment, the concave portion of the surface of the dosage form is at least 5%, more preferably at least 10% or at least 15%, still more preferably at least 20% or at least 25%, yet more preferably at least 30% or at least 35%, most preferably at least 40% or at least 45% and in particular at least 50% or at least 55%, based on the sum of concave portions, convex portions and planar portions.

In a preferred embodiment of the pharmaceutical dosage form according to the invention, the maximum extension of the dosage form orthogonal to the main area of extension of the dosage form is spaced from the centre of mass of the dosage form parallel to said main area of extension. For the purpose of the specification, the main area of extension of the dosage form is preferably the largest plain area that can be placed along a cut of the body of the dosage form. Preferably, the closest distance from the maximum extension of the dosage form orthogonal to the main area of extension of the dosage form to the centre of mass of the dosage form is at least 0.5 mm, more preferably at least 1.0 mm, still more preferably at least 1.5 mm, yet more preferably at least 2.0 mm, most preferably at least 2.5 mm and in particular at least 3.0 mm.



In a preferred embodiment, the cross sectional area of the pharmaceutical dosage form that is orthogonal to the longitudinal direction of extension and that contains the centre of mass of the dosage form has a shape so that at least 50%, more preferably at least 60% and in particular at least 75% of its area is spaced at least 0.2 mm, at least 0.3 mm, at least 0.4 mm or at least 0.5 mm, more preferably at least 0.6 mm, at least 0.7 mm, at least 0.8 mm or at least 0.9 mm, still more preferably at least 1.0 mm, at least 1.1 mm, at least 1.2 mm or at least 1.3 mm, yet more preferably at least 1.4 mm, at least 1.5 mm, at least 1.6 mm or at least 1.7 mm, most preferably at least 1.8 mm, at least 1.9 mm, at least 2.0 mm or at least 2.1 mm and in particular at least 2.2 mm, at least 2.3 mm, at least 2.4 mm or at least 2.5 mm from the centre of mass. Preferably, said cross sectional area contains the centre of mass.

In a preferred embodiment of the pharmaceutical dosage form according to the invention, the closest distance of each and every geometrical point within the dosage form to the surface of the dosage form is at most 10 mm, at most 9 mm, at most 8 mm or at most 7.5 mm; more preferably at most 7.0 mm, at most 6.5 mm or at most 6.0 mm; still more preferably at most 5.8 mm, at most 5.6 mm, at most 5.4 mm, at most 5.2 mm or at most 5.0 mm; yet more preferably at most 4.8 mm, at most 4.6 mm, at most 4.4 mm, at most 4.2 mm or at most 4.0 mm; yet more preferably at most 3.8 mm, at most 3.6 mm, at most 3.4 mm, at most 3.2 mm or at most 3.0 mm; most preferably at most 2.8 mm, at most 2.6 mm, at most 2.4 mm, at most 2.2 mm or at most 2.0 mm; and in particular at most 1.8 mm, at most 1.6 mm, at most 1.4 mm, at most 1.2 mm or at most 1.0 mm.

In a preferred embodiment, the centre of mass of the pharmaceutical dosage form lies within the main area of extension of the dosage form. Preferably, the pharmaceutical dosage form is symmetric about its main area of extension.

In a preferred embodiment, the surface  $S$  [ $\text{mm}^2$ ] to weight  $W$  [mg] ratio  $S / W$  of the pharmaceutical dosage form according to the invention is at least  $0.50 \text{ mm}^2/\text{mg}$ . Preferably,  $S / W$  is at least 0.51, at least 0.52, at least 0.53, at least 0.54 or at least 0.55; more preferably at least 0.56, at least 0.57, at least 0.58, at least 0.59 or at least 0.60; still more preferably at least 0.61, at least 0.62, at least 0.63, at least 0.64 or at least 0.65; yet more preferably at least 0.66, at least 0.67, at least 0.68, at least 0.69 or at least 0.70; most preferably at least 0.705, at least 0.710, at least 0.715, at least 0.720, at least 0.725, at least 0.730, at least 0.735, at least 0.740, at least 0.745 or at least 0.750; and in particular at least 0.755, at least 0.760, at least 0.765, at least 0.770, at least 0.775, at least 0.780, at least 0.785, at least 0.790, at least 0.795 or at least  $0.80 \text{ mm}^2/\text{mg}$ . In another preferred embodiment, the surface  $S$  [ $\text{mm}^2$ ] to weight  $W$  [mg] ratio  $S / W$  of the pharmaceutical dosage form

according to the invention is at least  $0.80 \text{ mm}^2/\text{mg}$ . Preferably,  $S / W$  is at least 0.81, at least 0.82, at least 0.83, at least 0.84 or at least 0.85; more preferably at least 0.86, at least 0.87, at least 0.88, at least 0.89 or at least 0.90; still more preferably at least 0.91, at least 0.92, at least 0.93, at least 0.94 or at least 0.95; yet more preferably at least 0.96, at least 0.97, at least 0.98, at least 0.99 or at least 1.00; most preferably at least 1.05, at least 1.10, at least 1.15, at least 1.20, at least 1.25, at least 1.30, at least 1.35, at least 1.40, at least 1.45 or at least 1.50; and in particular at least 1.55, at least 1.60, at least 1.65, at least 1.70, or at least  $1.75 \text{ mm}^2/\text{mg}$ .

In a preferred embodiment, the pharmaceutical dosage form according to the invention has a total surface  $S$  defined by the formula

$$S \geq A \cdot W^{2/3},$$

wherein  $A$  is at least 4.5, i.e.  $S \geq 4.5 \cdot W^{2/3}$ .

For example, when the pharmaceutical dosage form according to the invention has a total weight of 623 mg, its total surface  $S$  is preferably at least  $328 \text{ mm}^2$  ( $4.5 \cdot 623^{2/3}$ ) and when the pharmaceutical dosage form according to the invention has a total weight of 983 mg, its total surface  $S$  is preferably at least  $445 \text{ mm}^2$  ( $4.5 \cdot 983^{2/3}$ ).

Methods for measuring the total surface of a pharmaceutical dosage form are known to the skilled artisan. For example, the total surface may be calculated from the three dimensional extension of the pharmaceutical dosage form based on simple geometrical considerations (cf., e.g., Eudragit® Application Guidelines, 10th edition, 07/2007, Röhm GmbH, Darmstadt).

In approximation, the pharmaceutical dosage form may also be mentally divided into a plurality of identical cubic volume elements of suitable size (voxels) and the total surface may be determined by counting the squared area elements (pixels) being located at the surface.

Preferably, when measuring the total surface of the pharmaceutical dosage form, the micro-fine structure of the pharmacologically active compound ( $A$ ) and of all other constituents of the dosage form including polymers and pharmaceutical excipients, e.g. their porosity, is not taken into account. For the purpose of the specification, the term "surface" of the pharmaceutical dosage form preferably refers to the macroscopic surface (outer dimensions, silhouette). In other words, for the purpose of determining the surface of the pharmaceutical dosage form, the surface structure is preferably considered perfectly smooth.

In a preferred embodiment of the pharmaceutical dosage form according to the invention, A is 4.6, 4.7, 4.8, 4.9, 5.0, 5.1, 5.2, 5.3, 5.4, 5.5, 5.6, 5.7, 5.8, 5.9 or 6.0; more preferably 6.05, 6.1, 6.15, 6.2, 6.25, 6.3, 6.35, 6.4, 6.45, 6.5, 6.55, 6.6, 6.65, 6.7, 6.75, 6.8, 6.85, 6.9, 6.95, 7.0, 7.05, 7.1, 7.15, 7.2, 7.25, 7.3, 7.35, 7.4, 7.45 or 7.5.

In another preferred embodiment of the pharmaceutical dosage form according to the invention, A is 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, 8.7, 8.8, 8.9 or 9.0; more preferably 9.1, 9.2, 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9, 10.0, 10.1, 10.2, 10.3, 10.4 or 10.5; most preferably 10.6, 10.7, 10.8, 10.9, 11.0, 11.1, 11.2, 11.3, 11.4, 11.5, 11.6, 11.7, 11.8, 11.9 or 12.0; and in particular 12.1, 12.2, 12.3, 12.4, 12.5, 12.6, 12.7, 12.8, 12.9, 13.0, 13.1, 13.2, 13.3, 13.4 or 13.5.

In a preferred embodiment, the total surface S of the pharmaceutical dosage form according to the invention satisfies the following requirement

$$B \cdot W^{\frac{2}{3}} \geq S \geq A \cdot W^{\frac{2}{3}}$$

where

A and W are defined as above and

B is at most 20, more preferably at most 19, still more preferably at most 18, yet more preferably at most 17, most preferably at most 16 and in particular at most 15.

In a preferred embodiment, the total surface S of the pharmaceutical dosage form according to the invention is at least 50 mm<sup>2</sup>, at least 75 mm<sup>2</sup>, at least 100 mm<sup>2</sup>, at least 125 mm<sup>2</sup>, at least 150 mm<sup>2</sup>, at least 175 mm<sup>2</sup> or at least 200 mm<sup>2</sup>; more preferably at least 225 mm<sup>2</sup>, at least 250 mm<sup>2</sup>, at least 275 mm<sup>2</sup>, at least 300 mm<sup>2</sup>, at least 325 mm<sup>2</sup>, at least 350 mm<sup>2</sup>, at least 375 mm<sup>2</sup> or at least 400 mm<sup>2</sup>; still more preferably at least 425 mm<sup>2</sup>, at least 450 mm<sup>2</sup>, at least 475 mm<sup>2</sup>, at least 500 mm<sup>2</sup>, at least 525 mm<sup>2</sup>; at least 550 mm<sup>2</sup>, at least 575 mm<sup>2</sup> or at least 600 mm<sup>2</sup>; yet more preferably at least 625 mm<sup>2</sup>, at least 650 mm<sup>2</sup>, at least 675 mm<sup>2</sup>, at least 700 mm<sup>2</sup>, at least 725 mm<sup>2</sup>, at least 750 mm<sup>2</sup>, at least 775 mm<sup>2</sup> or at least 800 mm<sup>2</sup>; most preferably at least 825 mm<sup>2</sup>, at least 850 mm<sup>2</sup>, at least 875 mm<sup>2</sup>, at least 900 mm<sup>2</sup>, at least 925 mm<sup>2</sup>, at least 950 mm<sup>2</sup>, at least 975 mm<sup>2</sup> or at least 1000 mm<sup>2</sup>; and in particular at least 1025 mm<sup>2</sup>, at least 1050 mm<sup>2</sup>, at least 1075 mm<sup>2</sup>, at least 1100 mm<sup>2</sup>, at least 1125 mm<sup>2</sup>, at least 1150 mm<sup>2</sup>, at least 1175 mm<sup>2</sup> or at least 1200 mm<sup>2</sup>.

In a preferred embodiment, the total surface S of the pharmaceutical dosage form according to the invention is at most 1500 mm<sup>2</sup>, more preferably at most 1400 mm<sup>2</sup>, still more

preferably at most  $1300 \text{ mm}^2$ , yet more preferably at most  $1200 \text{ mm}^2$ , most preferably at most  $1100 \text{ mm}^2$ , and in particular at most  $1000 \text{ mm}^2$ .

In a preferred embodiment, at least 35% of the outer surface of the pharmaceutical dosage form according to the invention originates from cut surfaces of the extrudate, whereas the remainder originates from the jacket (barrel) of the extrudate. Preferably, at least 40% or at least 45%, more preferably at least 50% or at least 55%, still more preferably at least 60% or at least 65%, yet more preferably at least 70% or at least 72.5%, most preferably at least 75% or at least 77.5% and in particular at least 80% or at least 82.5% of the outer surface of the pharmaceutical dosage form according to the invention originates from cut surfaces of the extrudate.

In a preferred embodiment the pharmaceutical dosage form according to the invention is manufactured, particularly shaped, by means of a so-called H-plunger. The silhouette of a dosage form obtainable by means of such a H-plunger is schematically illustrated in Figure 4. H-plungers of suitable size and shape are commercially available. Typically, the volume and the surface of the dosage forms that are obtainable by a given H-plunger can be calculated with a formula usually provided by the manufacturer of the H-plunger.

For example, Notter GmbH, Germany offers a H-plunger forming a volume of  $94.3 + 171.6 h$  [ $\text{mm}^3$ ] and a surface of  $382 + 52.3 h$  [ $\text{mm}^2$ ], where  $h$  is the height of the dosage form (corresponding to distance  $b_2$  in Figure 4). Therefore, for example, when shaping 650 mg of a compacted composition having an overall density of  $1.000 \text{ mg/mm}^3$  with such H-plunger, a dosage form is obtained having a height of  $h = (650 - 94.3)/171.6 = 3.24 \text{ mm}$ . Thus, said dosage form has a surface of  $382 + 52.3 \cdot 3.24 = 551 \text{ mm}^2$ . When  $A = 4.5$ , the requirement of  $551 \text{ mm}^2 \geq 4.5 \cdot 650^{2/3}$  ( $= 337.6 \text{ mm}^2$ ) is satisfied. When  $A$  is about 7.3, the requirement of  $551 \text{ mm}^2 \geq 7.3 \cdot 650^{2/3}$  ( $= 547 \text{ mm}^2$ ) is still satisfied, but when  $A$  is 7.4, the requirement  $551 \text{ mm}^2 \geq 7.4 \cdot 650^{2/3}$  ( $= 555 \text{ mm}^2$ ) is not satisfied.

In a preferred embodiment, the pharmaceutical dosage form according to the invention has a total weight  $W$  of at least 50 mg, at least 75 mg, at least 100 mg, at least 125 mg or at least 150 mg; more preferably at least 175 mg, at least 200 mg, at least 225 mg, at least 250 mg or at least 275 mg; still more preferably at least 300 mg, at least 325 mg, at least 350 mg, at least 375 mg or at least 400 mg; yet more preferably at least 425 mg, at least 450 mg, at least 475 mg, at least 500 mg or at least 525 mg; most preferably at least 550 mg, at least 575 mg, at least 600 mg, at least 625 mg or at least 650 mg; and in particular at least 675 mg, at least 700 mg, at least 725 mg, at least 750 mg or at least 775 mg. Preferably, the total

weight of the pharmaceutical dosage form according to the invention is within the range from 0.01 g to 1.5 g, more preferably 0.05 g to 1.2 g, still more preferably 0.1 g to 1.0 g, most preferably 0.2 g to 0.9 g and in particular 0.25 g to 0.8 g.

In a preferred embodiment, the core of the pharmaceutical dosage form according to the invention has a morphological orientation caused by hot-melt extrusion that is substantially orthogonal to the longitudinal direction of extension of the dosage form.

In this regard, "substantially" means that the angle may somewhat deviate from  $90.0^\circ$ . Preferably, the angle is within the range of  $90\pm 30^\circ$ , more preferably  $90\pm 25^\circ$ , still more preferably  $90\pm 20^\circ$ , yet more preferably  $90\pm 15^\circ$ , most preferably  $90\pm 10^\circ$ , and in particular  $90\pm 5^\circ$ .

Analytical methods to determine the morphological orientation caused by hot-melt extrusion are known to the person skilled in the art such as electron microscopy, atomic force spectroscopy and the like. Another suitable method is the three-dimensional terahertz spectroscopy, e.g., terahertz time-domain spectroscopy (THz-TDS) (cf. e.g. S.L. Dexheimer, Terahertz Spectroscopy: Principles and Applications (Optical Science and Engineering Series), CRC; 1 edition 2007; R.E. Miles et al., Terahertz Frequency Detection and Identification of Materials and Objects (NATO Science for Peace and Security Series B: Physics and Biophysics), Springer; 1 edition 2007; and Y.-S. Lee et al., Principles of Terahertz Science and Technology (Lecture Notes in Physics), Springer; 1 edition 2008).

Figure 5A illustrates how the morphological orientation of an extrudate can be visualized by means of terahertz spectroscopy. Figure 5B illustrates that said morphological orientation can still be visualized after press-forming said extrudate, e.g. into tablets having a different outer shape.

Preferably, the core of the pharmaceutical dosage form according to the invention has a morphological orientation caused by hot-melt extrusion that is not only substantially orthogonal (perpendicular) to the longitudinal direction of extension of the dosage form, but additionally substantially orthogonal (perpendicular) to the transversal direction of extension of the dosage form.

In this regard, "substantially" also means that the angle may somewhat deviate from  $90.0^\circ$ . Preferably, the angle is within the range of  $90\pm 30^\circ$ , more preferably  $90\pm 25^\circ$ , still more

preferably  $90\pm 20^\circ$ , yet more preferably  $90\pm 15^\circ$ , most preferably  $90\pm 10^\circ$ , and in particular  $90\pm 5^\circ$ .

In a preferred embodiment the pharmaceutical dosage form according to the invention has an overall density of at least  $0.80$  or at least  $0.85\text{ g/cm}^3$ , more preferably at least  $0.90$  or at least  $0.95\text{ g/cm}^3$ , still more preferably at least  $1.00$ , at least  $1.05$  or at least  $1.10\text{ g/cm}^3$ , most preferably in the range from  $0.80$  to  $1.35\text{ g/cm}^3$ , and in particular in the range from  $0.95$  to  $1.25\text{ g/cm}^3$ .

In a preferred embodiment, the pharmaceutical dosage form according to the invention has an overall density within the range of  $1.00\pm 0.30\text{ g/cm}^3$ , more preferably  $1.00\pm 0.25\text{ g/cm}^3$ , still more preferably  $1.00\pm 0.20\text{ g/cm}^3$ , yet more preferably  $1.00\pm 0.15\text{ g/cm}^3$ , most preferably  $1.00\pm 0.10\text{ g/cm}^3$ , and in particular  $1.00\pm 0.05\text{ g/cm}^3$ . In another preferred embodiment, the pharmaceutical dosage form according to the invention has an overall density within the range of  $1.10\pm 0.30\text{ g/cm}^3$ , more preferably  $1.10\pm 0.25\text{ g/cm}^3$ , still more preferably  $1.10\pm 0.20\text{ g/cm}^3$ , yet more preferably  $1.10\pm 0.15\text{ g/cm}^3$ , most preferably  $1.10\pm 0.10\text{ g/cm}^3$ , and in particular  $1.10\pm 0.05\text{ g/cm}^3$ . In still another preferred embodiment, the pharmaceutical dosage form according to the invention has an overall density within the range of  $1.20\pm 0.30\text{ g/cm}^3$ , more preferably  $1.20\pm 0.25\text{ g/cm}^3$ , still more preferably  $1.20\pm 0.20\text{ g/cm}^3$ , yet more preferably  $1.20\pm 0.15\text{ g/cm}^3$ , most preferably  $1.20\pm 0.10\text{ g/cm}^3$ , and in particular  $1.20\pm 0.05\text{ g/cm}^3$ . Preferably, the overall density of the pharmaceutical dosage form according to the invention is  $1.00\pm 0.02\text{ g/cm}^3$ ,  $1.02\pm 0.02\text{ g/cm}^3$ ,  $1.04\pm 0.02\text{ g/cm}^3$ ,  $1.06\pm 0.02\text{ g/cm}^3$ ,  $1.08\pm 0.02\text{ g/cm}^3$ ,  $1.10\pm 0.02\text{ g/cm}^3$ ,  $1.12\pm 0.02\text{ g/cm}^3$ ,  $1.14\pm 0.02\text{ g/cm}^3$ ,  $1.16\pm 0.02\text{ g/cm}^3$ ,  $1.18\pm 0.02\text{ g/cm}^3$ ,  $1.20\pm 0.02\text{ g/cm}^3$ ,  $1.22\pm 0.02\text{ g/cm}^3$ ,  $1.24\pm 0.02\text{ g/cm}^3$ ,  $1.26\pm 0.02\text{ g/cm}^3$ ,  $1.28\pm 0.02\text{ g/cm}^3$ ,  $1.30\pm 0.02\text{ g/cm}^3$ ,  $1.32\pm 0.02\text{ g/cm}^3$ ,  $1.34\pm 0.02\text{ g/cm}^3$ ,  $1.36\pm 0.02\text{ g/cm}^3$ ,  $1.38\pm 0.02\text{ g/cm}^3$ , or  $1.40\pm 0.02\text{ g/cm}^3$ .

Preferably, the pharmaceutical dosage form according to the invention is characterized by a comparatively homogeneous distribution of density. Preferably, the densities of two segments of the pharmaceutical dosage form having a volume of  $1.0\text{ mm}^3$  each, deviate from one another by not more than  $\pm 10\%$ , more preferably not more than  $\pm 7.5\%$ , still more preferably not more than  $\pm 5.0\%$ , most preferably not more than  $\pm 2.5\%$ , and in particular not more than  $\pm 1.0\%$ . When the pharmaceutical dosage form is film coated, said two segments of the pharmaceutical dosage form having a volume of  $1.0\text{ mm}^3$  each are preferably segments of the core, i.e. do not contain any coating material.

The pharmaceutical dosage form according to the invention shows controlled release of the pharmacologically active ingredient (A) contained therein.

In a preferred embodiment, the release per area of the pharmacologically active ingredient (A) from the pharmaceutical dosage form according to the invention is faster through the front side and the opposite back side than through the circumferential rim.

A skilled person knows how to measure the release rate of the pharmacologically active ingredient (A) through the individual surfaces of the pharmaceutical dosage form according to the invention. For example, the pharmaceutical dosage form can be covered by an inert varnish that does not dissolve in the release medium. Only a distinct portion of the outer surface of the pharmaceutical dosage form having a well defined size and shape is left uncoated, e.g. by transiently covering said portion when applying the varnish or by mechanically removing the varnish at the desired location.

Alternatively, the pharmaceutical dosage form can be clamped in a suitable device so that only one particular side of the pharmaceutical dosage form (front side, back side and a portion of the circumferential rim, respectively) is contacted with the release medium.

In order to avoid diffusion length effects on the release profile, which effects are due to the shape of the dosage form but not due to the individual release properties of the material under investigation, preferably only the initial release is monitored, e.g. the release after 10, 20, 30, 45 or 60 minutes.

In a preferred embodiment, the dosage form according to the invention releases the pharmacologically active ingredient (A) under *in vitro* conditions in artificial gastric juice according to the following release profile:

- after 0.5 h at least 5 wt.-%,
- after 1 h at least 10 wt.-%,
- after 3 h at least 20 wt.-%,
- after 6 h at least 35 wt.-%, and
- after 12 h at least 55 wt.-%,

based on the total weight of the pharmacologically active ingredient (A) initially contained in the dosage form.

Preferably, the pharmaceutical dosage form according to the invention is adapted for oral administration. It is also possible, however, to administer the pharmaceutical dosage form via

different routes and thus, the pharmaceutical dosage form may alternatively be adapted for buccal, lingual, rectal or vaginal administration. Implants are also possible.

In a preferred embodiment, the pharmaceutical dosage form according to the invention is adapted for administration once daily. In another preferred embodiment, the pharmaceutical dosage form according to the invention is adapted for administration twice daily. In still another preferred embodiment, the pharmaceutical dosage form according to the invention is adapted for administration thrice daily.

For the purpose of the specification, "twice daily" means equal time intervals, i.e., every 12 hours, or different time intervals, e.g., 8 and 16 hours or 10 and 14 hours, between the individual administrations.

For the purpose of the specification, "thrice daily" means equal time intervals, i.e., every 8 hours, or different time intervals, e.g., 6, 6 and 12 hours; or 7, 7 and 10 hours, between the individual administrations.

Preferably, the pharmaceutical dosage form according to the invention effects an at least partially delayed release of the pharmacologically active compounds (A).

Delayed release is understood according to the invention preferably to mean a release profile in which the pharmacologically active compound (A) is released over a relatively long period with reduced intake frequency with the purpose of extended therapeutic action. This is achieved in particular with peroral administration. The expression "at least partially delayed release" covers according to the invention any pharmaceutical dosage forms which ensure modified release of the pharmacologically active compounds (A) contained therein. The pharmaceutical dosage forms preferably comprise coated or uncoated pharmaceutical dosage forms, which are produced with specific auxiliary substances, by particular processes or by a combination of the two possible options in order purposefully to change the release rate or location of release.

In the case of the pharmaceutical dosage forms according to the invention, the release time profile may be modified e.g. as follows: extended release, repeat action release, prolonged release and sustained release.

For the purpose of the specification "extended release" preferably means a product in which the release of active compound is delayed for a finite lag time, after which release is



unhindered. For the purpose of the specification "repeat action release" preferably means a product in which a first portion of active compound is released initially, followed by at least one further portion of active compound being released subsequently. For the purpose of the specification "prolonged release" preferably means a product in which the rate of release of active compound from the formulation after administration has been reduced, in order to maintain therapeutic activity, to reduce toxic effects, or for some other therapeutic purpose. For the purpose of the specification "sustained release" preferably means a way of formulating a medicine so that it is released into the body steadily, over a long period of time, thus reducing the dosing frequency. For further details, reference may be made, for example, to K.H. Bauer, Lehrbuch der Pharmazeutischen Technologie, 6th edition, WVG Stuttgart, 1999; and European Pharmacopoeia.

The pharmaceutical dosage form according to the invention may comprise one or more pharmacologically active compounds (A) at least in part in a further delayed-release form, wherein delayed release may be achieved with the assistance of conventional materials and processes known to the person skilled in the art, for example by embedding the substance in a delayed-release matrix or by applying one or more delayed-release coatings. Substance release must, however, be controlled such that addition of delayed-release materials does not impair the necessary breaking strength. Controlled release from the pharmaceutical dosage form according to the invention is preferably achieved by embedding the substance in a matrix. Component (C) may serve as such a matrix. The auxiliary substances acting as matrix materials control release. Matrix materials may, for example, be hydrophilic, gel-forming materials, from which release proceeds mainly by diffusion, or hydrophobic materials, from which release proceeds mainly by diffusion from the pores in the matrix.

Preferably, under physiological conditions the pharmaceutical dosage form according to the invention has released after 30 minutes 0.1 to 75%, after 240 minutes 0.5 to 95%, after 480 minutes 1.0 to 100% and after 720 minutes 2.5 to 100% of the pharmacologically active compound (A). Further preferred release profiles  $R_1$  to  $R_5$  are summarized in the table here below [all data in wt.-% of released pharmacologically active compound (A)]:

time	$R_1$	$R_2$	$R_3$	$R_4$	$R_5$
60 min	0-30	0-50	0-50	15-25	20-50
120 min	0-40	0-75	0-75	25-40	40-75
240 min	3-55	3-95	10-95	40-70	60-95
480 min	10-65	10-100	35-100	60-90	80-100
720 min	20-75	20-100	55-100	70-100	90-100
960 min	30-88	30-100	70-100	>80	
1440 min	50-100	50-100	>90		
2160 min	>80	>80			

Preferably, under *in vitro* conditions the pharmaceutical dosage form has released after 0.5 h 1.0 to 35 wt.-%, after 1 h 5.0 to 45 wt.-%, after 2 h 10 to 60 wt.-%, after 4 h at least 15 wt.-%, after 6 h at least 20 wt.-%, after 8 h at least 25 wt.-% and after 12 h at least 30 wt.-% of the pharmacologically active compound (A) that was originally contained in the pharmaceutical dosage form.

Suitable *in vitro* conditions are known to the skilled artisan. In this regard it can be referred to, e.g., the European Pharmacopoeia and to the experimental section. Preferably, the release profile is measured under the following conditions: Paddle apparatus equipped with sinker, 50 rpm,  $37 \pm 5$  °C, 900 mL simulated intestinal fluid pH 6.8 (phosphate buffer). In a preferred embodiment, to rotational speed of the paddle is increased to 100 rpm.

Preferably, the release profile of the pharmaceutical dosage form according to the present invention is stable upon storage, preferably upon storage at elevated temperature, e.g. 37°C, for 3 months in sealed containers. In this regard "stable" means that when comparing the initial release profile with the release profile after storage, at any given time point the release profiles deviate from one another by not more than 20%, more preferably not more than 15%, still more preferably not more than 10%, yet more preferably not more than 7.5%, most preferably not more than 5.0% and in particular not more than 2.5%.

The pharmaceutical dosage form according to the invention contains a pharmacologically active compound (A), for the purpose of the specification also referred to as "component (A)". The pharmacologically active ingredient (A) is embedded in a matrix comprising a polymer (C).

In a preferred embodiment, under ambient conditions, the solubility of component (A) in pure water is at least 1.0 g/L, more preferably at least 5.0 g/L, still more preferably at least 10 g/L, yet more preferably at least 25 g/L, most preferably at least 50 g/L and in particular at least 100 g/L.

In another preferred embodiment, under ambient conditions, the solubility of component (A) in pure water is at most 1.0 g/L, more preferably at most 0.5 g/L, still more preferably at most 0.1 g/L, yet more preferably at most 0.05 g/L, most preferably at most 0.01 g/L and in particular at most 0.005 g/L.

The pharmaceutical dosage form according to the invention contains a pharmaceutically effective amount of a pharmacologically active compound (A), which justifies use of the

pharmaceutical dosage form as a pharmaceutical preparation and is the cause of the activity thereof. Pharmacologically active compounds (A) which may in principle be considered in the pharmaceutical dosage form according to the invention are any known pharmaceutical substances, wherein these substances may be present in the pharmaceutical dosage form according to the invention as such, in the form the derivatives thereof, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the corresponding salts or solvates thereof, as racemates or in a form enriched in one or more stereoisomers (enantiomers or diastereomers).

The pharmaceutical dosage form according to the invention is suitable for the administration of a number of pharmacologically active compounds (A) in a single pharmaceutical dosage form. Preferably, the pharmaceutical dosage form contains only one particular pharmacologically active compound (A).

The amount of the pharmacologically active compound (A), based on the total amount of the pharmaceutical dosage form, is preferably within the range from 0.01 to 95 wt.-%, more preferably from 0.5 to 80 wt.-%, still more preferably 1.0 to 70 wt.-%, most preferably 5.0 to 60 wt.-% and in particular 10 to 50 wt.-%. In a preferred embodiment it is more than 20 wt.-%.

In a preferred embodiment the pharmaceutical dosage form according to the invention contains a psychotropically acting substance as the pharmacologically active compound (A).

The person skilled in the art knows which substances have a psychotropic action. Substances which influence psychological processes commonly have a psychotropic action, i.e. they act specifically on psychological functions. Substances with a psychotropic action may thus influence mood, either raising or lowering it. For the purpose of the description, substances with a psychotropic action include in particular opioids, stimulants, tranquillisers (e.g. barbiturates and benzodiazepines) and other narcotics. Substances with a psychotropic action preferably comprise substances which, in particular when improperly administered (in particular with the intention of abuse), cause an accelerated increase in active compound levels relative to proper oral administration, giving the abuser the desired effect, namely the "kick" or "rush". This kick is also obtained if the powdered pharmaceutical dosage form is administered nasally, i.e. is sniffed. Substances with a psychotropic action are preferably substances which (in the appropriate dose and pharmaceutical dosage form and when administered appropriately) influence human mental activity and/or sensory perception in such a way that they are fundamentally suited to abuse.

Preferably, the pharmacologically active ingredient (A) is an opioid.

In particular, the pharmaceutical dosage form according to the invention preferably contains a psychotropically acting substance selected from the group consisting of opioids [A07DA, N01AH, N02A, R05DA, R05FA,]; barbiturates [N01AF, N01AG, N03AA]; benzodiazepine derivatives [N03AE]; agents for treating opiate dependency [N07BC]; anxiolytics [N05B]; hypnotics and sedatives [N05C]; psychostimulants, agents for treating attention-deficit/hyperactivity disorder (ADHD) and nootropics [N06B]; antiemetics [A04A]; antiobesity preparations excluding diet products [A08A]; centrally acting muscle relaxants [M03B]; and antidotes [V03AB]. The abbreviations stated in square brackets here correspond to the ATC Index ("Gelbe Liste"), as used by the WHO for classifying pharmaceutical substances (preferred version: 2007 or 2008).

The pharmaceutical dosage form according to the invention preferably contains a psychotropically acting substance selected from the group consisting of opioids, vanilloid receptor modulators, serotonin/norepinephrine/dopamine modulators, GABA modulators, NMDA antagonists, ion channel blockers/modulators, cannabionoids, and other NSAIDS.

The following opiates, opioids, tranquillizers or other narcotics are substances with a psychotropic action, i.e. have a potential of abuse, and hence are preferably contained in the pharmaceutical dosage form according to the invention: alfentanil, allobarbitol, allylprodine, alphaprodine, alprazolam, amfepramone, amphetamine, amphetaminil, amobarbital, anileridine, apocodeine, axomadol, barbital, bemidone, benzylmorphine, bezitramide, bromazepam, brotizolam, buprenorphine, butobarbital, butorphanol, camazepam, carfentanil, cathine/D-norpseudoephedrine, chlordiazepoxide, clobazam, clofedanol, clonazepam, clonitazene, clorazepate, clotiazepam, cloxazolam, cocaine, codeine, cyclobarbitol, cyclorphan, cyprenorphine, delorazepam, desomorphine, dextromoramide, dextropropoxyphene, dezocine, diampromide, diamorphine, diazepam, dihydrocodeine, dihydromorphine, dihydromorphone, dimenoxadol, dimephetamol, dimethylthiambutene, dioxaphetylbutyrate, dipipanone, dronabinol, eptazocine, estazolam, ethoheptazine, ethylmethylthiambutene, ethyl loflazepate, ethylmorphine, etonitazene, etorphine, fencamfamine, fenethylline, fenpipramide, fenproporex, fentanyl, fludiazepam, flunitrazepam, flurazepam, halazepam, haloxazolam, heroin, hydrocodone, hydromorphone, hydroxypethidine, isomethadone, hydroxymethylmorphinan, ketazolam, ketobemidone, levacetylmethadol (LAAM), levomethadone, levorphanol, levophenacylmorphane, levoxemacin, lisdexamfetamine dimesylate, lofentanil, loprazolam, lorazepam, lormetazepam, mazindol, medazepam,

mefenorex, meperidine, meprobamate, metapon, meptazinol, metazocine, methylmorphine, metamphetamine, methadone, methaqualone, 3-methylfentanyl, 4-methylfentanyl, methylphenidate, methylphenobarbital, methyprylon, metopon, midazolam, modafinil, morphine, myrophine, nabilone, nalbuphene, nalorphine, narceine, nicomorphine, nimetazepam, nitrazepam, nordazepam, norlevorphanol, normethadone, normorphine, norpipanone, opium, oxazepam, oxazolam, oxycodone, oxymorphone, Papaver somniferum, papaveretum, pernoline, pentazocine, pentobarbital, pethidine, phenadoxone, phenomorphane, phenazocine, phenoperidine, piminodine, pholcodeine, phenmetrazine, phenobarbital, phentermine, pinazepam, pipradrol, piritramide, prazepam, profadol, proheptazine, promedol, properidine, propoxyphene, remifentanil, secbutabarbital, secobarbital, sufentanil, tapentadol, temazepam, tetrazepam, tilidine (cis and trans), tramadol, triazolam, vinylbital, N-(1-methyl-2-piperidinoethyl)-N-(2-pyridyl)propionamide, (1R,2R)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (1R,2R,4S)-2-(dimethylamino)methyl-4-(p-fluorobenzyloxy)-1-(m-methoxyphenyl)cyclohexanol, (1R,2R)-3-(2-dimethylaminomethyl-cyclohexyl)phenol, (1S,2S)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)phenol, (2R,3R)-1-dimethylamino-3-(3-methoxyphenyl)-2-methyl-pentan-3-ol, (1RS,3RS,6RS)-6-dimethylaminomethyl-1-(3-methoxyphenyl)-cyclohexane-1,3-diol, preferably as racemate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(4-isobutyl-phenyl)propionate, 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)phenyl 2-(6-methoxy-naphthalen-2-yl)propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(4-isobutyl-phenyl)propionate, 3-(2-dimethylaminomethyl-cyclohex-1-enyl)-phenyl 2-(6-methoxy-naphthalen-2-yl)propionate, (RR-SS)-2-acetoxy-4-trifluoromethylbenzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-trifluoromethylbenzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-4-chloro-2-hydroxybenzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methylbenzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-4-methoxybenzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2-hydroxy-5-nitrobenzoic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, (RR-SS)-2',4'-difluoro-3-hydroxy-biphenyl-4-carboxylic acid 3-(2-dimethylaminomethyl-1-hydroxy-cyclohexyl)-phenyl ester, and corresponding stereoisomeric compounds, in each case the corresponding derivatives thereof, physiologically acceptable enantiomers, stereoisomers, diastereomers and racemates and the physiologically acceptable derivatives thereof, e.g. ethers, esters or amides, and in each case the physiologically acceptable compounds thereof, in particular the salts thereof and solvates, e.g. hydrochlorides.

In a preferred embodiment the pharmaceutical dosage form according to the invention contains an opioid selected from the group consisting of DPI-125, M6G (CE-04-410), ADL-5859, CR-665, NRP290 and sebacoyl dinalbuphine ester.

In a preferred embodiment the pharmaceutical dosage form according to the invention contains one pharmacologically active compound (A) or more pharmacologically active compounds (A) selected from the group consisting of oxymorphone, hydromorphone and morphine, or the physiologically acceptable compounds thereof, in particular the salts thereof and solvates.

In another preferred embodiment, the pharmacologically active compound (A) is selected from the group consisting of tapentadol, fexeladol and axomadol, or the physiologically acceptable compounds thereof, in particular the salts thereof and solvates.

In a preferred embodiment the pharmaceutical dosage form according to the invention contains one pharmacologically active compound (A) or more pharmacologically active compounds (A) selected from the group consisting of 1,1-(3-dimethylamino-3-phenyl-pentamethylen)-6-fluor-1,3,4,9-tetrahydropyrano[3,4-b]indole, in particular its hemicitrate; 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylen]-1,3,4,9-tetrahydropyrano[3,4-b]indole, in particular its citrate; and 1,1-[3-dimethylamino-3-(2-thienyl)pentamethylen]-1,3,4,9-tetrahydropyrano[3,4-b]-6-fluoro-indole, in particular its hemicitrate. These compounds are known, for example, from WO 2004/043967 or WO 2005/066183. The corresponding descriptions are hereby introduced as a reference and are deemed to be part of the disclosure.

For the purposes of the description, the pharmacokinetic parameters, which may be determined from the blood plasma concentrations of the pharmacologically active compound (A), are defined as follows:

$C_{\max}$	maximum measured plasma concentration of the active ingredient after single administration ( $\equiv$ average <i>peak plasma level</i> )
$t_{\max}$	interval of time from administration of the active ingredient until $C_{\max}$ is reached
$t_{1/2}$	half-life
$AUC_{0-\infty}$	total area under the curve

The above parameters are in each case stated as mean values of the individual values for all investigated patients/test subjects.

A person skilled in the art knows how the pharmacokinetic parameters of the active ingredient may be calculated from the measured concentrations of the active ingredient in

the blood plasma. In this connection, reference may be made, for example, to Willi Cawello (ed.) *Parameters for Compartment-free Pharmacokinetics*, Shaker Verlag Aachen (1999).

In a preferred embodiment, after preferably oral administration of the dosage form according to the invention, *in vivo* the average *peak plasma level* ( $C_{\max}$ ) is on average reached after  $t_{\max}$   $4.0 \pm 2.5$  h, more preferably after  $t_{\max}$   $4.0 \pm 2.0$  h, still more preferably after  $t_{\max}$   $4.0 \pm 1.5$  h, most preferably after  $t_{\max}$   $4.0 \pm 1.0$  h and in particular after  $t_{\max}$   $4.0 \pm 0.5$  h. In another preferred embodiment, after preferably oral administration of the dosage form according to the invention, *in vivo* the average *peak plasma level* ( $C_{\max}$ ) is on average reached after  $t_{\max}$   $5.0 \pm 2.5$  h, more preferably after  $t_{\max}$   $5.0 \pm 2.0$  h, still more preferably after  $t_{\max}$   $5.0 \pm 1.5$  h, most preferably after  $t_{\max}$   $5.0 \pm 1.0$  h and in particular after  $t_{\max}$   $5.0 \pm 0.5$  h. In still another preferred embodiment, after preferably oral administration of the dosage form according to the invention, *in vivo* the average *peak plasma level* ( $C_{\max}$ ) is on average reached after  $t_{\max}$   $6.0 \pm 2.5$  h, more preferably after  $t_{\max}$   $6.0 \pm 2.0$  h, still more preferably after  $t_{\max}$   $6.0 \pm 1.5$  h, most preferably after  $t_{\max}$   $6.0 \pm 1.0$  h and in particular after  $t_{\max}$   $6.0 \pm 0.5$  h.

In a preferred embodiment, the average value for  $t_{1/2}$  after preferably oral administration of the dosage form according to the invention *in vivo* is  $4.3 \pm 2.5$  h, more preferably  $4.3 \pm 2.0$  h, still more preferably  $4.3 \pm 1.5$  h, most preferably  $4.3 \pm 1.0$  h, and in particular  $4.3 \pm 0.5$  h. In another preferred embodiment, the average value for  $t_{1/2}$  after preferably oral administration of the dosage form according to the invention *in vivo* is preferably  $5.3 \pm 2.5$  h, more preferably  $5.3 \pm 2.0$  h, still more preferably  $5.3 \pm 1.5$  h, most preferably  $5.3 \pm 1.0$  h, and in particular  $5.3 \pm 0.5$  h. In still another preferred embodiment, the average value for  $t_{1/2}$  after preferably oral administration of the dosage form according to the invention *in vivo* is preferably  $6.3 \pm 2.5$  h, more preferably  $6.3 \pm 2.0$  h, still more preferably  $6.3 \pm 1.5$  h, most preferably  $6.3 \pm 1.0$  h, and in particular  $6.3 \pm 0.5$  h.

In a preferred embodiment, the pharmacologically active compound (A) is tapentadol or a physiologically acceptable salt thereof, and after preferably oral administration of the dosage form according to the invention, *in vivo* the average value for the total area under the curve  $AUC_{0-\infty}$  is  $825 \pm 600$  ng·h/mL, more preferably  $825 \pm 500$  ng·h/mL, still more preferably  $825 \pm 400$  ng·h/mL, yet more preferably  $825 \pm 300$  ng·h/mL, most preferably  $825 \pm 200$  ng·h/mL, and in particular  $825 \pm 100$  ng·h/mL. In another preferred embodiment, the pharmacologically active compound (A) is tapentadol or a physiologically acceptable salt thereof, and after preferably oral administration of the dosage form according to the invention, *in vivo* the average value for the total area under the curve  $AUC_{0-\infty}$  is  $1100 \pm 600$  ng·h/mL, more preferably  $1100 \pm 500$  ng·h/mL, still more preferably  $1100 \pm 400$  ng·h/mL, yet more preferably

1100  $\pm$  300 ng·h/mL, most preferably 1100  $\pm$  200 ng·h/mL, and in particular 1100  $\pm$  100 ng·h/mL.

In a preferred embodiment, the pharmacologically active compound (A) is tapentadol or a physiologically acceptable salt thereof, and after preferably oral administration of the dosage form according to the invention, *in vivo* the average value of  $C_{\max}$  is 63  $\pm$  40 ng/mL, more preferably 63  $\pm$  30 ng/mL, still more preferably 63  $\pm$  20 ng/mL, yet more preferably 63  $\pm$  15 ng/mL, most preferably 63  $\pm$  10 ng/mL and in particular 63  $\pm$  5 ng/mL. In another preferred embodiment, the pharmacologically active compound (A) is tapentadol or a physiologically acceptable salt thereof, and after preferably oral administration of the dosage form according to the invention, *in vivo* the average value of  $C_{\max}$  is 89  $\pm$  40 ng/mL, more preferably 89  $\pm$  30 ng/mL, still more preferably 89  $\pm$  20 ng/mL, yet more preferably 89  $\pm$  15 ng/mL, most preferably 89  $\pm$  10 ng/mL and in particular 89  $\pm$  5 ng/mL.

In a particularly preferred embodiment the pharmacologically active compound (A) is tapentadol or a physiologically acceptable salt thereof and the pharmaceutical dosage form according to the invention is bioequivalent to a formulation that contains tapentadol or a physiologically acceptable salt thereof in a dosage of 200 mg and 250 mg, respectively, and is characterized by the following pharmacokinetic data:

Parameter	dosage 200 mg	dosage 250 mg
$AUC_{0-\infty}$	825 ng·h/mL	1096 ng·h/mL
$C_{\max}$	62.5 ng/mL	89.3 ng/mL
$t_{\max}$	5.00 h	5.00 h
$t_{1/2}$	5.2 h	5.4 h

The skilled person is aware what requirements have to be satisfied in order to achieve bioequivalence. In this regard it can be referred e.g. to "Note for Guidance on the Investigation of Bioavailability and Bioequivalence", EMEA, London, 26 July 2001 (CPMP/EWP/QWP/1401/98); "Guidance for Industry - Bioavailability and Bioequivalence - Studies for Orally Administered Drug Products - General Considerations", FDA, BP, Announced in the Federal Register: Volume 68, Number 53/March 19, 2003; and "Guidance for Industry - Statistical Approaches to Establishing Bioequivalence", FDA, BP, January 2001.

In general, two medicinal products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives and if their bioavailabilities after administration in the same molar dose are similar to such degree that their effects, with respect to both efficacy and safety, will be essentially the same. Preferably, statistical data should be analyzed using



ANOVA based on a 90% confidence interval. For example, as regards AUC-ratio, the 90% confidence interval for this measure of relative bioavailability should lie within an acceptance interval of 0.80-1.25, and as regards  $C_{\max}$ -ratio, the 90% confidence interval for this measure of relative bioavailability should lie within an acceptance interval of 0.80-1.25.

In a preferred embodiment, the pharmaceutical dosage form according to the invention contains no substances which irritate the nasal passages and/or pharynx, i.e. substances which, when administered via the nasal passages and/or pharynx, bring about a physical reaction which is either so unpleasant for the patient that he/she does not wish to or cannot continue administration, for example burning, or physiologically counteracts taking of the corresponding active compound, for example due to increased nasal secretion or sneezing. Further examples of substances which irritate the nasal passages and/or pharynx are those which cause burning, itching, an urge to sneeze, increased formation of secretions or a combination of at least two of these stimuli. Corresponding substances and the quantities thereof which are conventionally to be used are known to the person skilled in the art. Some of the substances which irritate the nasal passages and/or pharynx are accordingly based on one or more constituents or one or more plant parts of a hot substance drug. Corresponding hot substance drugs are known per se to the person skilled in the art and are described, for example, in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd., revised edition, Gustav Fischer Verlag, Stuttgart-New York, 1982, pages 82 et seq.. The corresponding description is hereby introduced as a reference and is deemed to be part of the disclosure.

The pharmaceutical dosage form according to the invention furthermore preferably contains no antagonists for the pharmacologically active compound (A), preferably no antagonists against psychotropic substances, in particular no antagonists against opioids. Antagonists suitable for a given pharmacologically active compound (A) are known to the person skilled in the art and may be present as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof. The pharmaceutical dosage form according to the invention preferably contains no antagonists selected from among the group comprising naloxone, naltrexone, nalmefene, nalide, nalmexone, nalorphine or naluphine, in each case optionally in the form of a corresponding physiologically acceptable compound, in particular in the form of a base, a salt or solvate; and no neuroleptics, for example a compound selected from among the group comprising haloperidol, promethazine, fluphenazine, perphenazine, levomepromazine, thioridazine,

perazine, chlorpromazine, chlorprothixine, zuclopenthixol, flupentixol, prothipendyl, zotepine, benperidol, pipamperone, melperone and bromperidol.

The pharmaceutical dosage form according to the invention furthermore preferably contains no emetic. Emetics are known to the person skilled in the art and may be present as such or in the form of corresponding derivatives, in particular esters or ethers, or in each case in the form of corresponding physiologically acceptable compounds, in particular in the form of the salts or solvates thereof. The pharmaceutical dosage form according to the invention preferably contains no emetic based on one or more constituents of ipecacuanha (ipecac) root, for example based on the constituent emetine, as are, for example, described in "Pharmazeutische Biologie - Drogen und ihre Inhaltsstoffe" by Prof. Dr. Hildebert Wagner, 2nd, revised edition, Gustav Fischer Verlag, Stuttgart, New York, 1982. The corresponding literature description is hereby introduced as a reference and is deemed to be part of the disclosure. The pharmaceutical dosage form according to the invention preferably also contains no apomorphine as an emetic.

Finally, the pharmaceutical dosage form according to the invention preferably also contains no bitter substance. Bitter substances and the quantities effective for use may be found in US-2003/0064099 A1, the corresponding disclosure of which should be deemed to be the disclosure of the present application and is hereby introduced as a reference. Examples of bitter substances are aromatic oils, such as peppermint oil, eucalyptus oil, bitter almond oil, menthol, fruit aroma substances, aroma substances from lemons, oranges, limes, grapefruit or mixtures thereof, and/or denatonium benzoate.

The pharmaceutical dosage form according to the invention accordingly preferably contains neither substances which irritate the nasal passages and/or pharynx, nor antagonists for the pharmacologically active compound (A), nor emetics, nor bitter substances.

The pharmaceutical dosage form according to the invention is characterized by a comparatively homogeneous distribution of the pharmacologically active compound (A). Preferably, the content of the pharmacologically active compound (A) in two segments of the pharmaceutical dosage form having a volume of  $1.0 \text{ mm}^3$  each, deviates from one another by not more than  $\pm 10\%$ , more preferably not more than  $\pm 7.5\%$ , still more preferably not more than  $\pm 5.0\%$ , most preferably not more than  $\pm 2.5\%$ , and in particular not more than  $\pm 1.0\%$ . When the pharmaceutical dosage form is film coated, said two segments of the pharmaceutical dosage form having a volume of  $1.0 \text{ mm}^3$  each are preferably segments of the core, i.e. do not contain any coating material.

Preferably, all components of the pharmaceutical dosage form according to the invention have a comparatively homogeneous distribution within the pharmaceutical dosage form. Preferably, the content of each component in two segments of the pharmaceutical dosage form having a volume of  $1.0 \text{ mm}^3$  each, deviates from one another by not more than  $\pm 10\%$ , more preferably not more than  $\pm 7.5\%$ , still more preferably not more than  $\pm 5.0\%$ , most preferably not more than  $\pm 2.5\%$ , and in particular not more than  $\pm 1.0\%$ . When the pharmaceutical dosage form is film coated, said two segments of the pharmaceutical dosage form having a volume of  $1.0 \text{ mm}^3$  each are preferably segments of the core, i.e. do not contain any coating material.

Preferably, the pharmaceutical dosage form according to the invention contains at least one polymer (C), for the purpose of the specification also referred to as "component (C)". Preferably, the pharmaceutical dosage form contains at least one synthetic, semi-synthetic or natural polymer (C), which contributes considerably to the elevated breaking strength (resistance to crushing) of the pharmaceutical dosage form. For the purpose of the specification a "semi-synthetic" product has been produced by chemical manipulation of naturally occurring substances.

Preferably, the mechanical properties of the pharmaceutical dosage form according to the invention, particularly its breaking strength, substantially rely on the presence of polymer (C), although its mere presence does not suffice in order to achieve said properties. The advantageous properties of the pharmaceutical dosage form according to the invention, in particular also its mechanical properties, may not automatically be achieved by simply hot-melt extruding the pharmacologically active compound (A), polymer (C), and optionally further excipients by means of conventional methods for the preparation of pharmaceutical dosage forms by hot-melt extrusion. In fact, usually suitable extruders must be selected for the preparation and critical extrusion parameters must be adjusted, particularly pressure/force, temperature and time. Thus, even if conventional extruders are used, the process protocols usually must be adapted in order to meet the required criteria.

Preferably, polymer (C) is water-soluble. Preferably, polymer (C) is substantially unbranched.

Polymer (C) may comprise a single type of polymer having a particular average molecular weight, or a mixture (blend) of different polymers, such as two, three, four or five polymers, e.g., polymers of the same chemical nature but different average molecular weight, polymers

of different chemical nature but same average molecular weight, or polymers of different chemical nature as well as different molecular weight.

Individual or combinations of polymers may be selected from the group comprising polyalkylene oxide, preferably polymethylene oxide, polyethylene oxide, polypropylene oxide; polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyvinylpyrrolidone, poly(alk)acrylate, poly(hydroxy fatty acids), such as for example poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (Biopol®), poly(hydroxyvaleric acid); polycaprolactone, polyvinyl alcohol, polyesteramide, polyethylene succinate, polylactone, polyglycolide, polyurethane, polyamide, polylactide, polyacetal (for example polysaccharides optionally with modified side chains), polylactide/glycolide, polylactone, polyglycolide, polyorthoester, polyanhydride, block polymers of polyethylene glycol and polybutylene terephthalate (Polyactive®), polyanhydride (Polifeprosan), copolymers thereof, block-copolymers thereof, and mixtures of at least two of the stated polymers, or other polymers with the above characteristics.

Preferably, polymer (C) comprises a polyalkylene oxide, more preferably a polyethylene oxide, a polypropylene oxide, an ethylene oxide-propylene oxide copolymerisate, which may be e.g. a random copolymer, alternating copolymer or block copolymer, or a mixture of any of the foregoing.

Particularly preferred are high molecular weight polymers with a preferably weight average molecular weight ( $M_w$ ) or viscosity average molecular weight ( $M_\eta$ ) of at least of at least  $0.1 \cdot 10^6$  g/mol, of at least  $0.2 \cdot 10^6$  g/mol, of at least  $0.5 \cdot 10^6$  g/mol, of at least  $1.0 \cdot 10^6$  g/mol, of at least  $2.5 \cdot 10^6$  g/mol, of at least  $5.0 \cdot 10^6$  g/mol, of at least  $7.5 \cdot 10^6$  g/mol or of at least  $10 \cdot 10^6$  g/mol, preferably  $1.0 \cdot 10^6$  g/mol to  $15 \cdot 10^6$  g/mol. Suitable methods for determining  $M_w$  or  $M_\eta$  are known to the person skilled in the art. Preferably,  $M_\eta$  is determined using rheological measurements and  $M_w$  is determined using gel permeation chromatography (GPC) on suitable phases.

Preferably, the molecular weight dispersity  $M_w/M_n$  of polymer (C) is within the range of  $2.5 \pm 2.0$ , more preferably  $2.5 \pm 1.5$ , still more preferably  $2.5 \pm 1.0$ , yet more preferably  $2.5 \pm 0.8$ , most preferably  $2.5 \pm 0.6$ , and in particular  $2.5 \pm 0.4$ .

The polymers preferably have a viscosity at 25°C of 4,500 to 17,600 cP, measured in a 5 wt.-% aqueous solution using a model RVF Brookfield viscosimeter (spindle no. 2 / rotational speed 2 rpm), of 400 to 4,000 cP, measured on a 2 wt.-% aqueous solution using the stated

viscosimeter (spindle no. 1 or 3 / rotational speed 10 rpm) or of 1,650 to 10,000 cP, measured on a 1 wt.-% aqueous solution using the stated viscosimeter (spindle no. 2 / rotational speed 2 rpm).

Most preferred are thermoplastic polyalkylene oxides having a weight average molecular weight ( $M_w$ ) or a viscosity average molecular weight ( $M_v$ ) of at least  $0.2 \cdot 10^6$  g/mol, more preferably at least  $0.3 \cdot 10^6$  g/mol, still more preferably at least  $0.4 \cdot 10^6$  g/mol, yet more preferably at least  $0.5 \cdot 10^6$  g/mol, most preferably at least  $1.0 \cdot 10^6$  g/mol and in particular within the range of  $1.0 \cdot 10^6$  to  $15 \cdot 10^6$  g/mol are preferred, e.g. polyethylene oxides, polypropylene oxides or the (block-)copolymers thereof.

In a preferred embodiment according to the invention the polymer (C) comprises

- a polyalkylene oxide having a weight average molecular weight ( $M_w$ ) or viscosity average molecular weight ( $M_v$ ) of at least  $0.2 \cdot 10^6$  g/mol

in combination with

- at least one further polymer, preferably but not necessarily also having a weight average molecular weight ( $M_w$ ) or viscosity average molecular weight ( $M_v$ ) of at least  $0.2 \cdot 10^6$  g/mol, selected from the group consisting of polyethylene, polypropylene, polyvinyl chloride, polycarbonate, polystyrene, polyacrylate, poly(hydroxy fatty acids), polycaprolactone, polyvinyl alcohol, polyesteramide, polyethylene succinate, polylactone, polyglycolide, polyurethane, polyvinylpyrrolidone, polyamide, polylactide, polylactide/glycolide, polylactone, polyglycolide, polyorthoester, polyanhydride, block polymers of polyethylene glycol and polybutylene terephthalate, polyanhydride, polyacetal, cellulose esters, cellulose ethers and copolymers thereof. Cellulose esters and cellulose ethers are particularly preferred, e.g. methylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, carboxymethylcellulose, and the like.

In a preferred embodiment, said further polymer is neither a polyalkylene oxide nor a polyalkylene glycol. Nonetheless, the pharmaceutical dosage form may contain polyalkylene glycol, e.g. as plasticizer, but then, the pharmaceutical dosage form preferably is a ternary mixture of polymers: component (C) + further polymer + plasticizer.

In a particularly preferred embodiment, said further polymer is a hydrophilic cellulose ester or cellulose ether, preferably hydroxypropylmethylcellulose, preferably having an average viscosity of  $100,000 \pm 50,000$  mPas, more preferably  $100,000 \pm 20,000$  mPas.

Preferably, the content of said further polymer amounts to 0.5 to 25 wt.-%, more preferably 1.0 to 20 wt.-%, still more preferably 2.0 to 17.5 wt.-%, yet more preferably 3.0 to 15 wt.-% and most preferably 4.0 to 12.5 wt.-% and in particular 5.0 to 10 wt.-%, based on the total weight of the polyalkylene oxide.

In a preferred embodiment the relative weight ratio of said polyalkylene oxide and said further polymer is within the range of from 20:1 to 1:20, more preferably 10:1 to 1:10, still more preferably 7:1 to 1:5, yet more preferably 5:1 to 1:1, most preferably 4:1 to 1.5:1 and in particular 3:1 to 2:1.

Preferably, the content of said further polymer amounts to 0.5 to 25 wt.-%, more preferably 1.0 to 20 wt.-%, still more preferably 2.0 to 22.5 wt.-%, yet more preferably 3.0 to 20 wt.-% and most preferably 4.0 to 17.5 wt.-% and in particular 5.0 to 15 wt.-%, based on the total weight of the pharmaceutical dosage form.

It is not intended to be bound by any theory, but it is believed that the further polymer may serve as a supplementary matrix material that guarantees a minimal retardant effect on the release of the pharmacologically active compound (A) even if the molecular chains of the polyalkylene oxide have been partially damaged in the course of the manufacture of the pharmaceutical dosage form, e.g. by extrusion, thereby decreasing the average molecular weight. Furthermore, it seems that the further polymer contributes to the storage stability of the dosage form, particularly with respect to its release profile.

Physiologically acceptable, hydrophobic materials which are known to the person skilled in the art may be used as supplementary matrix materials. Polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins are preferably used as hydrophilic matrix materials. Ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the salts, amides or esters thereof are very particularly preferably used as matrix materials. Matrix materials prepared from hydrophobic materials, such as hydrophobic polymers, waxes, fats, long-chain fatty acids, fatty alcohols or corresponding esters or ethers or mixtures thereof are also preferred. Mono- or diglycerides of C<sub>12</sub>-C<sub>30</sub> fatty acids and/or C<sub>12</sub>-C<sub>30</sub> fatty alcohols and/or waxes or mixtures thereof are particularly preferably used as hydrophobic materials. It is also possible to use mixtures of the above-stated hydrophilic and hydrophobic materials as matrix materials.

Preferably, the overall content of polymer (C) is at least 5 wt.-%, at least 10 wt.-%, at least 15 wt.-% or at least 20 wt.-%, more preferably at least 30 wt.-%, still more preferably at least 40 wt.-%, most preferably at least 50 wt.-% and in particular at least 60 wt.-%, of the total weight of the pharmaceutical dosage form. In a preferred embodiment the content of the polymer (C) is within the range of from about 20 to about 49 wt.-% of the total weight of the pharmaceutical dosage form.

In a preferred embodiment, the overall content of polymer (C) is within the range of  $25 \pm 20$  wt.-%, more preferably  $25 \pm 15$  wt.-%, most preferably  $25 \pm 10$  wt.-%, and in particular  $25 \pm 5$  wt.-%. In another preferred embodiment, the overall content of polymer (C) is within the range of  $35 \pm 20$  wt.-%, more preferably  $35 \pm 15$  wt.-%, most preferably  $35 \pm 10$  wt.-%, and in particular  $35 \pm 5$  wt.-%. In still another preferred embodiment, the overall content of polymer (C) is within the range of  $45 \pm 20$  wt.-%, more preferably  $45 \pm 15$  wt.-%, most preferably  $45 \pm 10$  wt.-%, and in particular  $45 \pm 5$  wt.-%. In yet another preferred embodiment, the overall content of polymer (C) is within the range of  $55 \pm 20$  wt.-%, more preferably  $55 \pm 15$  wt.-%, most preferably  $55 \pm 10$  wt.-%, and in particular  $55 \pm 5$  wt.-%. In a further preferred embodiment, the overall content of polymer (C) is within the range of  $65 \pm 20$  wt.-%, more preferably  $65 \pm 15$  wt.-%, most preferably  $65 \pm 10$  wt.-%, and in particular  $65 \pm 5$  wt.-%. In still a further a preferred embodiment, the overall content of polymer (C) is within the range of  $75 \pm 20$  wt.-%, more preferably  $75 \pm 15$  wt.-%, most preferably  $75 \pm 10$  wt.-%, and in particular  $75 \pm 5$  wt.-%.

In a preferred embodiment, polymer (C) is homogeneously distributed in the pharmaceutical dosage form according to the invention. Preferably, polymer (C) forms a matrix in which the pharmacologically active compound (A) is embedded. In a particularly preferred embodiment, the pharmacologically active compound (A) and polymer (C) are intimately homogeneously distributed in the pharmaceutical dosage form so that the pharmaceutical dosage form does not contain any segments where either pharmacologically active compound (A) is present in the absence of polymer (C) or where polymer (C) is present in the absence of pharmacologically active compound (A).

When the pharmaceutical dosage form is film coated, the polymer (C) is preferably homogeneously distributed in the core of the pharmaceutical dosage form, i.e. the film coating preferably does not contain polymer (C). Nonetheless, the film coating as such may of course contain one or more polymers, which however, preferably differ from the polymer (C) contained in the core.

The dosage form according to the invention exhibits a breaking strength of at least 300 N, typically measured along the longitudinal direction of extension of the dosage form.

The "breaking strength" (resistance to crushing) of a pharmaceutical dosage form is known to the skilled person. In this regard it can be referred to, e.g., W.A. Ritschel, *Die Tablette*, 2. Auflage, Editio Cantor Verlag Aulendorf, 2002; H Liebermann et al., *Pharmaceutical dosage forms: Tablets*, Vol. 2, Informa Healthcare; 2 edition, 1990; and *Encyclopedia of Pharmaceutical Technology*, Informa Healthcare; 1 edition.

For the purpose of the specification, the breaking strength is preferably defined as the amount of force that is necessary in order to fracture the pharmaceutical dosage form (= breaking force). Therefore, for the purpose of the specification the dosage form does preferably not exhibit the desired breaking strength when it breaks, i.e., is fractured into at least two independent parts that are separated from one another. In another preferred embodiment, however, the pharmaceutical dosage form is regarded as being broken if the force decreases by 25% (threshold value) of the highest force measured during the measurement (see below).

The dosage forms according to the invention are distinguished from conventional dosage forms in that, due to their breaking strength, they cannot be pulverized by the application of force with conventional means, such as for example a pestle and mortar, a hammer, a mallet or other usual means for pulverization, in particular devices developed for this purpose (tablet crushers). In this regard "pulverization" means crumbling into small particles that would immediately release the pharmacologically active compound (A) in a suitable medium. Avoidance of pulverization virtually rules out oral or parenteral, in particular intravenous or nasal abuse.

Conventional tablets typically have a breaking strength well below 200 N in any direction of extension. The breaking strength of conventional round tablets may be estimated according to the following empirical formula: *Breaking Strength* [in N] =  $10 \times \text{Diameter Of The Tablet}$  [in mm]. Thus, according to said empirical formula, a round tablet having a breaking strength of at least 500 N would require a diameter of at least 50 mm (about 2 inches). Such a tablet, however, could not be swallowed. The above empirical formula does not apply to the pharmaceutical dosage forms of the invention, which are not conventional but rather special.

Further, the actual mean chewing force is about 220 N (cf., e.g., P.A. Proeschel et al., *J Dent Res*, 2002, 81(7), 464-468, copy attached). This means that conventional tablets having a



breaking strength well below 200 N may be crushed upon chewing, whereas the dosage forms according to the invention may not, at least not in direction of extension  $E_1$ .

Still further, when applying a gravitational acceleration of about  $9.81 \text{ m/s}^2$ , 300 N correspond to a gravitational force of more than 30 kg, i.e. the pharmaceutical dosage forms according to the invention can withstand a weight of more than 30 kg.

Methods for measuring the breaking strength of a pharmaceutical dosage form are known to the skilled artisan. Suitable devices are commercially available.

For example, the breaking strength (resistance to crushing) can be measured in accordance with the European Pharmacopoeia 5.0, 2.9.8 or 6.0, 2.09.08 "Resistance to Crushing of Tablets". The test is intended to determine, under defined conditions, the resistance to crushing of tablets, measured by the force needed to disrupt them by crushing. The apparatus consists of 2 jaws facing each other, one of which moves towards the other. The flat surfaces of the jaws are perpendicular to the direction of movement. The crushing surfaces of the jaws are flat and larger than the zone of contact with the tablet. The apparatus is calibrated using a system with a precision of 1 Newton. The tablet is placed between the jaws, taking into account, where applicable, the shape, the break-mark and the inscription; for each measurement the tablet is oriented in the same way with respect to the direction of application of the force (typically along the longitudinal direction of extension). The measurement is carried out on 10 tablets, taking care that all fragments of tablets have been removed before each determination. The result is expressed as the mean, minimum and maximum values of the forces measured, all expressed in Newton.

A similar description of the breaking strength (breaking force) can be found in the US Pharmacopoeia. The breaking strength can alternatively be measured in accordance with the method described therein where it is stated that the breaking strength is the force required to cause a tablet to fail (i.e., break) in a specific plane. The tablets are generally placed between two platens, one of which moves to apply sufficient force to the tablet to cause fracture. For conventional, round (circular cross-section) tablets, loading occurs across their diameter (sometimes referred to as diametral loading), and fracture occurs in the plane. The breaking force of tablets is commonly called hardness in the pharmaceutical literature; however, the use of this term is misleading. In material science, the term hardness refers to the resistance of a surface to penetration or indentation by a small probe. The term crushing strength is also frequently used to describe the resistance of tablets to the application of a compressive load. Although this term describes the true nature of the test more accurately

than does hardness, it implies that tablets are actually crushed during the test, which is often not the case.

Alternatively, the breaking strength (resistance to crushing) can be measured in accordance with WO 2006/082099, which can be regarded as a modification of the method described in the European Pharmacopoeia. The apparatus used for the measurement is preferably a "Zwick Z 2.5" materials tester,  $F_{\max} = 2.5$  kN with a maximum draw of 1150 mm, which should be set up with one column and one spindle, a clearance behind of 100 mm and a test speed adjustable between 0.1 and 800 mm/min together with testControl software. Measurement is performed using a pressure piston with screw-in inserts and a cylinder (diameter 10 mm), a force transducer,  $F_{\max} = 1$  kN, diameter = 8 mm, class 0.5 from 10 N, class 1 from 2 N to ISO 7500-1, with manufacturer's test certificate M according to DIN 55350-18 (Zwick gross force  $F_{\max} = 1.45$  kN) (all apparatus from Zwick GmbH & Co. KG, Ulm, Germany) with Order No BTC-FR 2.5 TH. D09 for the tester, Order No BTC-LC 0050N. P01 for the force transducer, Order No BO 70000 S06 for the centring device.

In a preferred embodiment of the invention, the breaking strength is measured by means of a breaking strength tester Sotax<sup>®</sup>, type HT100 (Allschwil, Switzerland). The Sotax<sup>®</sup> HT100 can measure the breaking strength according to two different measurement principles: constant speed (where the test jaw is moved at a constant speed adjustable from 5-200 mm/min) or constant force (where the test jaw increases force linearly adjustable from 5-100 N/sec). In principle, both measurement principles are suitable for measuring the breaking strength of the dosage form according to the invention. Preferably, the breaking strength is measured at constant speed, preferably at a constant speed of 120 mm/min.

In a preferred embodiment, the pharmaceutical dosage form is regarded as being broken if it is fractured into at least two separate pieces.

In another preferred embodiment, the pharmaceutical dosage form is regarded as being broken if the force decreases by 25% (threshold value) of the highest force measured during the measurement. For example, if the highest force measured during the measurement is 144 N, the tablet is regarded as being broken when the force decreases below 108 N (= 75% of 144 N; decrease by 25%). The value of the breaking strength in the respective direction of extension is then 144 N. In a preferred embodiment, said threshold value is 30%, more preferably 35%, still more preferably 40%, most preferably 45% and in particular 50%. Under these circumstances, a dosage form may have to be regarded as being broken although it has not been fractured into at least two separate pieces. For example, a dosage form that

has been torn in the middle but that has not been fragmented, may have to be regarded as being broken in accordance with this definition of the breaking strength. Thus, in accordance with this definition, failure of the breaking strength test at a particular force may be due to fracture of the dosage form or any other deformation that causes the force to drop below the above threshold value, e.g. rupture, cracking, dunting, cleaving, fissure, and the like.

The pharmaceutical dosage form according to the invention has a breaking strength of at least 300 N, preferably at least 400 N, more preferably at least 500 N, still more preferably at least 750 N, most preferably at least 1000 N and in particular at least 1500 N.

The pharmaceutical dosage form according to the invention exhibits mechanical strength over a wide temperature range, in addition to the breaking strength (resistance to crushing) optionally also sufficient hardness, impact resistance, impact elasticity, tensile strength and/or modulus of elasticity, optionally also at low temperatures (e.g. below -24 °C, below -40 °C or in liquid nitrogen), for it to be virtually impossible to pulverize by spontaneous chewing, grinding in a mortar, pounding, etc. Thus, preferably, the comparatively high breaking strength of the pharmaceutical dosage form according to the invention is maintained even at low or very low temperatures, e.g., when the pharmaceutical dosage form is initially chilled to increase its brittleness, for example to temperatures below -25°C, below -40 °C or even in liquid nitrogen.

The pharmaceutical dosage form according to the invention exhibits high impact strength.

For example, the falling impact strength of the pharmaceutical dosage forms is preferably about 0%. The falling impact strength is a breakage ratio obtained when a tablet is allowed to fall from the height of 50 cm onto a stainless steel plate and defined by:  $\frac{\{\text{broken tablets}\}}{\{\text{tested tablets}\}} \cdot 100(\%)$ .

Preferably, the impact strength of the pharmaceutical dosage form according to the invention is sufficiently high so that it cannot be comminuted by means of a hammer. Preferably, when applying five manual hammer strokes by means of a hammer having a weight of 500 g, the pharmaceutical dosage form cannot be comminuted. In a preferred embodiment, the pharmaceutical dosage form does not only exhibit this impact strength at ambient temperature, but also below +4°C (refrigerator), more preferably below -33°C (deep freezer), most preferably below -77°C (dry ice) and in particular below -190 °C (liquid nitrogen).

Preferably, the pharmaceutical dosage form according to the invention exhibits a cutting resistance of at least 75 N, more preferably at least 100 N, still more preferably at least 125 N, yet more preferably at least 140 N, most preferably at least 150 N and in particular at least 160 N, in at least one direction of extension, preferably in direction of extension  $E_1$ . Preferably, the cutting test is performed according to DIN EN ISO 604, preferably at a testing speed of 30 mm/min and by means of a universal glass cleaning blade having a thickness of 0.30 mm.

The friability of the pharmaceutical dosage form according to the invention can be measured, e.g., by means of a Pharmatest PTF-E apparatus (Hainburg, Germany) following, e.g., the European Pharmacopeia (Ph. Eur.) specifications. Preferably, the friability of the pharmaceutical dosage form according to the invention is at most 0.50%, more preferably at most 0.40%, still more preferably at most 0.30%, yet more preferably at most 0.20%, most preferably at most 0.10% and in particular at most 0.05%.

Preferably, the pharmaceutical dosage form according to the invention contains a coating, preferably a film-coating. Suitable coating materials are known to the skilled person. Suitable coating materials are commercially available, e.g. under the trademarks Opadry® and Eudragit®.

Examples of suitable materials include cellulose esters and cellulose ethers, such as methylcellulose (MC), hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylcellulose (HEC), sodium carboxymethylcellulose (Na-CMC), ethylcellulose (EC), cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose phthalate (HPMCP); poly(meth)acrylates, such as aminoalkylmethacrylate copolymers, ethylacrylate methylmethacrylate copolymers, methacrylic acid methylmethacrylate copolymers, methacrylic acid methylmethacrylate copolymers; vinyl polymers, such as polyvinylpyrrolidone, polyvinylacetatephthalate, polyvinyl alcohol, polyvinylacetate; and natural film formers, such as shellack.

In a particularly preferred embodiment, the coating is water-soluble. Preferably, the coating is based on polyvinyl alcohol, such as polyvinyl alcohol-part. hydrolyzed, and may additionally contain polyethylene glycol, such as macrogol 3350, and/or pigments.

The coating of the pharmaceutical dosage form can increase its storage stability.

The coating can be resistant to gastric juices and dissolve as a function of the pH value of the release environment. By means of this coating, it is possible to ensure that the pharmaceutical dosage form according to the invention passes through the stomach undissolved and the active compound is only released in the intestines. The coating which is resistant to gastric juices preferably dissolves at a pH value of between 5 and 7.5. Corresponding materials and methods for the delayed release of active compounds and for the application of coatings which are resistant to gastric juices are known to the person skilled in the art, for example from "Coated Pharmaceutical dosage forms - Fundamentals, Manufacturing Techniques, Biopharmaceutical Aspects, Test Methods and Raw Materials" by Kurt H. Bauer, K. Lehmann, Hermann P. Osterwald, Rothgang, Gerhart, 1st edition, 1998, Medpharm Scientific Publishers.

Besides the pharmacologically active compound (A) and polymer (C) the pharmaceutical dosage form according to the invention may contain further constituents, such as conventional pharmaceutical excipients.

In a preferred embodiment, the pharmaceutical dosage form contains at least one natural, semi-synthetic or synthetic wax (D), for the purpose of the specification also referred to as "component (D)". Preferred waxes are those with a softening point of at least 50 °C, more preferably of at least 55°C, still more preferably of at least 60 °C, most preferably of at least 65°C and in particular at least 70 °C.

Carnauba wax and beeswax are particularly preferred. Carnauba wax is very particularly preferred. Carnauba wax is a natural wax which is obtained from the leaves of the carnauba palm and has a softening point of at least 80 °C. When the wax component is additionally contained, its content is sufficiently high so that the desired mechanical properties of the pharmaceutical dosage form are achieved.

Auxiliary substances (B), further purpose of the specification also referred to as "component (B)", which may be contained in the pharmaceutical dosage form according to the invention are those known auxiliary substances which are conventional for the formulation of solid pharmaceutical dosage forms.

Examples of auxiliary substances (B) are plasticizers, (further) matrix materials, antioxidants and the like.

Suitable plasticizers include triacetin and polyethylene glycol, preferably a low molecular weight polyethylene glycol (e.g. macrogol 6000).

Matrix materials are auxiliary substances which influence active compound release, preferably hydrophobic or hydrophilic, preferably hydrophilic polymers, very particularly preferably hydroxypropylmethylcellulose, and/or antioxidants. Polymers, particularly preferably cellulose ethers, cellulose esters and/or acrylic resins are preferably contained as hydrophilic matrix materials. Ethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, hydroxymethylcellulose, poly(meth)acrylic acid and/or the derivatives thereof, such as the copolymers, salts, amides or esters thereof are very particularly preferably contained as matrix materials.

Suitable antioxidants are ascorbic acid, butylhydroxyanisole (BHA), butylhydroxytoluene (BHT), salts of ascorbic acid, monothioglycerol, phosphorous acid, vitamin C, vitamin E and the derivatives thereof, coniferyl benzoate, nordihydroguajaretic acid, gallus acid esters, sodium bisulfite, particularly preferably butylhydroxytoluene or butylhydroxyanisole and  $\alpha$ -tocopherol. The antioxidant is preferably used in quantities of 0.01 to 10 wt.-%, preferably of 0.03 to 5 wt.-%, relative to the total weight of the pharmaceutical dosage form.

In a preferred embodiment, the pharmaceutical dosage form according to the invention contains citric acid or a physiologically acceptable salt thereof.

Preferred compositions  $X_1$  to  $X_4$  of the pharmaceutical dosage form according to the invention are summarized in the table here below:

wt.-%	$X_1$	$X_2$	$X_3$	$X_4$
component (A)	26.5 $\pm$ 25	26.5 $\pm$ 20	26.5 $\pm$ 15	26.5 $\pm$ 13
polyalkylene oxide (e.g. PEO)	46.5 $\pm$ 25	46.5 $\pm$ 17	46.5 $\pm$ 12	46.5 $\pm$ 10
cellulose ester or ether (e.g. HPMC)	14 $\pm$ 7	14 $\pm$ 5	14 $\pm$ 2.5	14 $\pm$ 0.5
plasticizer (e.g. PEG)	12.5 $\pm$ 10	12.5 $\pm$ 7	12.5 $\pm$ 5	12.5 $\pm$ 3
antioxidant (e.g. $\alpha$ -tocopherol)	0.125 $\pm$ 0.12	0.125 $\pm$ 0.1	0.125 $\pm$ 0.05	0.125 $\pm$ 0.03

The pharmaceutical dosage form according to the invention is hot-melt extruded, i.e. produced by thermoforming with the assistance of an extruder, preferably without there being any observable consequent discoloration of the extrudate.

In order to investigate the extent of discoloration due to this thermoforming, the colour of the mixture of starting components of which the pharmaceutical dosage form consists is first determined without addition of a color-imparting component, such as for example a coloring pigment or an intrinsically colored component (for example  $\alpha$ -tocopherol). This composition is

then thermoformed according to the invention, wherein all process steps, including cooling of the extrudate, are performed under an inert gas atmosphere. By way of comparison, the same composition is produced by the same process, but without an inert gas atmosphere. The color of the pharmaceutical dosage form produced according to the invention from the starting composition and of the pharmaceutical dosage form produced by way of comparison is determined. The determination is performed with the assistance of "Munsell Book of Color" from Munsell Color Company Baltimore, Maryland, USA, 1966 edition. If the color of the pharmaceutical dosage form thermoformed according to the invention has a color with identification no. N 9.5, but at most a color with the identification no. 5Y 9/1, thermoforming is classed as being "without discoloration". If the pharmaceutical dosage form has a color with the identification no. 5Y 9/2 or greater, as determined according to the Munsell Book of Color, the thermoforming is classed as being "with discoloration".

In general, hot-melt extrusion comprises the steps of

- i) mixing components (A), (C), optionally (B) and/or (D),
- ii) heating the resultant mixture in the extruder at least up to the softening point of component (C) and extruding the thus heated mixture through the outlet orifice of the extruder by application of force,
- iii) singulating the still plastic extrudate and forming it into the pharmaceutical dosage form or
- iv) forming the cooled or optionally re-heated singulated extrudate into the pharmaceutical dosage form.

Mixing of the components according to process step i) may also proceed in the extruder.

Components (A), (C), optionally (B) and/or (D) may also be mixed in a mixer known to the person skilled in the art. The mixer may, for example, be a roll mixer, shaking mixer, shear mixer or compulsory mixer.

Before blending with the remaining components, component (C) and/or (D) is preferably provided according to the invention with an antioxidant. This may proceed by mixing the two components, (C) and the antioxidant, preferably by dissolving or suspending the antioxidant in a highly volatile solvent and homogeneously mixing this solution or suspension with component (C) and the optionally present component (D) and removing the solvent by drying, preferably under an inert gas atmosphere.

The, preferably molten, mixture which has been heated in the extruder at least up to the softening point of component (C) is extruded from the extruder through a die with at least one bore.

The process according to the invention requires the use of suitable extruders, preferably screw extruders. Screw extruders which are equipped with two screws (twin-screw-extruders) are particularly preferred.

A further aspect of the invention relates to process for the manufacture of a hot-melt extruded pharmaceutical dosage form, preferably as defined above, with controlled release of a pharmacologically active ingredient (A) as defined above embedded in a matrix comprising a polymer (C) as defined above, the dosage form having an oblong shape comprising a longitudinal direction of extension, a transversal direction of extension orthogonal to the longitudinal direction of extension, a front side, an opposite back side and a circumferential rim between said front and back side, comprising the steps of

(a) hot-melt extruding a mass comprising

- the pharmacologically active ingredient (A) and
- the polymer (C),

through an oblong die thereby obtaining an extrudate with an oblong cross-section;

(b) cutting said extrudate into slices (preferably in a plane substantially orthogonal to the direction of extrusion) having two opposing cut surfaces of oblong shape;

(c) placing said slices into a tableting tool comprising upper punch and lower punch in a manner so that the opposing surfaces of oblong shape face said upper and lower punch, respectively;

(d) press-forming dosage forms from the slices; and

(e) optionally, applying a film coating.

The extrusion is preferably performed so that the expansion of the strand due to extrusion is not more than 50%, i.e. that when using a die with a bore having a diameter of e.g. 6 mm, the extruded strand should have a diameter of not more than 9 mm. More preferably, the expansion of the strand is not more than 40%, still more preferably not more than 35%, most preferably not more than 30% and in particular not more than 25%. It has been surprisingly found that if the extruded material in the extruder is exposed to a mechanical stress exceeding a certain limit, a significant expansion of the strand occurs thereby resulting in



undesirable irregularities of the properties of the extruded strand, particularly its mechanical properties.

Preferably, extrusion is performed in the absence of water, i.e., no water is added. However, traces of water (e.g., caused by atmospheric humidity) may be present.

The extruder preferably comprises at least two temperature zones, with heating of the mixture at least up to the softening point of component (C) proceeding in the first zone, which is downstream from a feed zone and optionally mixing zone. The throughput of the mixture is preferably from 2.0 kg to 8.0 kg/hour.

After heating at least up to the softening point of component (C), the molten mixture is conveyed with the assistance of the screws, further homogenized, compressed or compacted such that, immediately before emerging from the extruder die, it exhibits a minimum pressure of 5 bar, preferably of at least 7.5 bar, more preferably at least 10 bar, still more preferably at least 12.5 bar, yet more preferably at least 15 bar, most preferably at least 17.5 bar and in particular at least 20 bar, and is extruded through the die as an extruded strand or strands, depending on the number of bores which the die comprises.

In a preferred embodiment, the die head pressure is within the range of from 25 to 85 bar. The die head pressure can be adjusted inter alia by die geometry, temperature profile and extrusion speed.

The casing of the extruder used according to the invention may be heated or cooled. The corresponding temperature control, i.e. heating or cooling, is so arranged that the mixture to be extruded exhibits at least an average temperature (product temperature) corresponding to the softening temperature of component (C) and does not rise above a temperature at which the pharmacologically active compound (A) to be processed may be damaged. Preferably, the temperature of the mixture to be extruded is adjusted to below 180 °C, preferably below 150 °C, but at least to the softening temperature of component (C). Typical extrusion temperatures are 120 °C and 130 °C.

In a preferred embodiment, the extruder torque is within the range of from 25 to 55 Nm. Extruder torque can be adjusted inter alia by die geometry, temperature profile and extrusion speed.

In step (a) of the process according to the invention a mass is hot-melt extruded through an oblong die thereby obtaining an extrudate with an oblong cross-section. In step (b) of the process according to the invention said extrudate obtained in step (a) is cut into slices having two opposing cut surfaces of oblong shape.



Thus, the die geometry predetermines the cross-section of the extrudate as well as the cross-section of the slices which both are oblong, preferably substantially identical.

The oblong cross-section preferably has a maximum lengthwise extension of 21 mm and a maximum crosswise extension of 10 mm.

In a preferred embodiment, the relative ratio of the maximum lengthwise extension to the maximum crosswise extension of the oblong die is at least 1.5 : 1, more preferably at least 2.0 : 1, still more preferably at least 2.2 : 1, yet more preferably at least 2.3 : 1, most preferably at least 2.4 : 1 and in particular at least 2.5 : 1.

Preferred oblong dies have the following lengthwise and crosswise extensions  $A_1$  to  $A_8$ :

[mm]	$A_1$	$A_2$	$A_3$	$A_4$	$A_5$	$A_6$	$A_7$	$A_8$
lengthwise	$16.5 \pm 4$	$16.5 \pm 2$	$15 \pm 2$	$15 \pm 1$	$15 \pm 0.5$	$18 \pm 2$	$18 \pm 1$	$18 \pm 0.5$
crosswise	$6 \pm 2$	$6 \pm 1.5$	$5 \pm 2$	$5 \pm 1$	$5 \pm 0.5$	$7 \pm 2$	$7 \pm 1$	$7 \pm 0.5$

Preferably, the oblong die has elliptic shape or rectangular shape, preferably with rounded edges of the rectangle, e.g.  or .

Preferably, the dimensions of the die are about 2 mm smaller than the corresponding dimensions of the final oblong dosage form.

After extrusion of the molten mixture and optional cooling of the extruded strand or extruded strands, the extrudates are preferably singulated. Singulation may preferably be performed by cutting up the extrudates by means of revolving or rotating knives, water jet cutters, wires, blades or with the assistance of laser cutters.

Singulation, e.g. cutting, yields slices of well defined length and weight having two opposing cut surfaces of oblong shape and a jacket (barrel). Typically, as a single dosage form is preferably formed from a single slice, each slice already contains the desired dosage of the pharmaceutically active ingredient (A) and the desired amount of polymer (C) as well as optionally present further excipients, which are also intended to be contained in the final dosage form.

In a preferred embodiment, singulation is performed in a plane substantially orthogonal to the direction of extrusion. However, it is also possible that the plane of singulation, e.g., includes an angle to the direction of extrusion. Singulation, e.g. cutting, yields slices of well defined size, particularly of well defined volume and surface area. The surface area is the sum of the two opposing cut surfaces of oblong shape and the area of the jacket (barrel).

In a preferred embodiment, at least 50 % of the total surface of the slices obtained in step (b) is formed by the two opposing cut surfaces, more preferably at least 55%, still more preferably at least 60%, yet more preferably at least 65%, most preferably at least 70% and in particular at least 75%.

In a preferred embodiment, the relative ratio of the area of the two cut surfaces S to the area of the jacket (barrel) of the slice (extrudate) is at least 0.1, 0.2, 0.3, 0.4 or 0.5; more preferably at least 0.6, 0.7, 0.8, 0.9 or 1.0; still more preferably at least 1.1, 1.2, 1.3, 1.4 or 1.5; yet more preferably at least 1.6, 1.7, 1.8, 1.9 or 2.0; most preferably at least 2.1, 2.2, 2.3, 2.4 or 2.5; and in particular at least 2.6, 2.7, 2.8, 2.9 or 3.0. In another preferred embodiment, the relative ratio of the area of the two cut surfaces S to the area of the jacket (barrel) of the slice (extrudate) is at least 3.1, 3.2, 3.3, 3.4 or 3.5; more preferably at least 3.6, 3.7, 3.8, 3.9 or 4.0; still more preferably at least 4.1, 4.2, 4.3, 4.4 or 4.5; yet more preferably at least 4.6, 4.7, 4.8, 4.9 or 5.0; most preferably at least 5.1, 5.2, 5.3, 5.4 or 5.5; and in particular at least 5.6, 5.7, 5.8, 5.9 or 6.0.

A skilled person recognizes that composition of the extruded mass, size of the extrusion die and length of the slices that are singulated from the extruded strand determine the total weight of the dosage form (except an optionally applied coating), the drug content of the dosage form as well as its release profile. Said release profile is based on the different release properties of the opposing cut surfaces of the slices, which will essentially provide the top side and the back side of the dosage form, and the jacket (barrel) of the slices, which will essentially provide the circumferential rim of the dosage form.

An inert gas atmosphere is not necessary for intermediate or final storage of the optionally singulated extrudate or the final shape of the pharmaceutical dosage form according to the invention.

The singulated extrudate may be pelletized with conventional methods or be press-formed into tablets in order to impart the final shape to the pharmaceutical dosage form. It is,

however, also possible not to singulate the extruded strands and, with the assistance of contrarotating calender rolls comprising opposing recesses in their outer sleeve, to form them into the final shape, preferably a tablet, and to singulate these by conventional methods.

Should the optionally singulated extrudate not immediately be formed into the final shape, but instead cooled for storage, after the period of storage an inert gas atmosphere, preferably a nitrogen atmosphere, should be provided and must be maintained during heating of the stored extrudate up until plasticization and definitive shaping to yield the pharmaceutical dosage form.

The application of force in the extruder onto the at least plasticized mixture is adjusted by controlling the rotational speed of the conveying device in the extruder and the geometry thereof and by dimensioning the outlet orifice in such a manner that the pressure necessary for extruding the plasticized mixture is built up in the extruder, preferably immediately prior to extrusion. The extrusion parameters which, for each particular composition, are necessary to give rise to a pharmaceutical dosage form with a resistance to crushing of at least 300 N, preferably of at least 400 N, more preferably at least 500 N, may be established by simple preliminary testing.

For example, hot-melt extrusion may be performed by means of a twin-screw-extruder type Micro 27 GL 40 D (Leistritz, Nürnberg, Germany), screw diameter 27 mm. Screws having eccentric ends may be used. A heatable die may be used. The entire extrusion process should be performed under nitrogen atmosphere. The extrusion parameters may be adjusted e.g. to the following values: rotational speed of the screws: 100 Upm; delivery rate: 4 kg/h; product temperature: 125°C; and jacket temperature: 120 °C.

Alternatively, hot-melt extrusion may be performed by means of a planetary-gear extruder. Planetary-gear extruders are known and described inter alia in detail in Handbuch der Kunststoff-Extrusionstechnik I (1989) "Grundlagen" in Chapter 1.2 "Klassifizierung von Extrudern", pages 4 to 6. A suitable planetary gear extruder is, for example, an extruder type BCG 10 (LBB Bohle, Ennigerloh, Germany) having four planetary spindles and an extrusion die. A gravimetric dosing of 3.0 kg/h is suitable. The extrusion may be performed, for example, at a rotational speed of 28,6 rpm and a product temperature of about 88°C.

The shaping of the pharmaceutical dosage form according to the invention is of particular importance. The final shape of the pharmaceutical dosage form may either be provided

during the hardening of the mixture by applying heat and force or in a subsequent step. In both cases, the mixture of all components is preferably in the plastified state, i.e. preferably, shaping is performed at a temperature at least above the softening point of component (C).

Shaping can be performed, e.g., by means of a tableting press comprising die and plunger (punch) of appropriate shape.

In a preferred embodiment, the plunger is an H-plunger so that the cross section of the pharmaceutical dosage form assumes the form of a H.

In another preferred embodiment, the plunger is a conventional oblong plunger yielding biconvex oblong tablets having a circumferential rim.

The process for the preparation of the pharmaceutical dosage form according to the invention is preferably performed continuously. Preferably, the process involves the extrusion of a homogeneous mixture comprising components (A) and (C). It is particularly advantageous if the obtained intermediate, e.g. the strand obtained by extrusion, exhibits uniform properties. Particularly desirable are uniform density, uniform distribution of the active compound, uniform mechanical properties, uniform porosity, uniform appearance of the surface, etc. Only under these circumstances the uniformity of the pharmacological properties, such as the stability of the release profile, may be ensured and the amount of rejects can be kept low. It has been surprisingly found that the above properties may be obtained by means of twin-screw-extruders and planetary-gear-extruders, twin-screw-extruders being particularly preferred.

It has been surprisingly found that the process according to the invention overcomes optical defects and a structural weakness that was observed in hot-melt extruded tablets manufactured from cylindrical extrusion strands having a circular cross-section and press-forming the extrudates by means of H-plungers.

It was surprisingly found that the resulting extrudates having oblong cross-section according to the invention are able to fill the tableting punch more perfectly and thus, solve the observed issues.

Further, it was found that when using an oblong die extrusion is smoothly possible without modifications of the parameters. Using an oblong-shaped extrusion die leads to a lower melt temperature and to a lower back pressure. This indicates a more polymer protecting process.

Thus, tableting leads to a superior quality, if the mass is hot-melt extruded through the oblong-shaped die, for "standard" (biconvex) oblong-shape as well as for H-shape. Resistance to crushing (breaking strength) is at least comparable or higher for tablets from oblong extrudates, the deformed H-shaped dosage forms show significantly less defects.

Still further, it has been surprisingly found that dissolution speeds up for tablets formed from oblong-shaped extrudates in comparison to that derived from cylindrical extrudates having a circular cross-section.

Summing up, extruding through oblong-shaped dies is advantageous if the extrudate is to be formed to an oblong-shaped tablet. In particular, typical defects of oblong H-shaped tablets can be overcome.

A further aspect of the invention relates to a hot-melt extruded pharmaceutical dosage form obtainable by the process described above.

A further aspect of the invention relates to a packaging containing the pharmaceutical dosage form according to the invention and an oxygen scavenger. Suitable packages include blister packages and bottles, such as glass bottles or bottles made from thermoplastic polymers.

Oxygen scavengers and the application thereof in pharmaceutical packaging are known to the skilled artisan. In a preferred embodiment, the oxygen scavenger is selected from the group consisting of metal-catalyzed oxidizable organic polymers and anti-oxidants. It has been surprisingly found that the storage stability of the pharmaceutical dosage form can be increased when keeping the oxygen content of the atmosphere within the packaging low. Methods for packaging pharmaceutical dosage forms and the application of suitable oxygen scavengers are known to the skilled artisan. In this regard it can be referred to e.g. D.A. Dean, *Pharmaceutical Packaging Technology*, Taylor & Francis, 1st ed.; F.A. Paine et al., *Packaging Pharmaceutical and Healthcare Products*, Springer, 1st ed.; and O.G. Piringer et al., *Plastic Packaging: Interactions with Food and Pharmaceuticals*, Wiley-VCH, 2nd ed.

The pharmaceutical dosage form according to the invention is suitable to avoid various misuses, particularly

- accidental misuse (e.g. unintentional);
- recreational misuse; and

- experienced drug misuse.

A further aspect of the invention relates to the use of an opioid for the manufacture of the pharmaceutical dosage form as described above for the treatment of pain.

A further aspect of the invention relates to the use of a pharmaceutical dosage form as described above for avoiding or hindering the abuse of the pharmacologically active compound (A) contained therein.

A further aspect of the invention relates to the use of a pharmaceutical dosage form as described above for avoiding or hindering the unintentional overdose of the pharmacologically active compound (A) contained therein.

In this regard, the invention also relates to the use of a pharmacologically active compound (A) as described above and/or a synthetic or natural polymer (C) as described above for the manufacture of the pharmaceutical dosage form according to the invention for the prophylaxis and/or the treatment of a disorder, thereby preventing an overdose of the pharmacologically active compound (A), particularly due to comminution of the pharmaceutical dosage form by mechanical action.

Further, the invention relates to a method for the prophylaxis and/or the treatment of a disorder comprising the administration of the pharmaceutical dosage form according to the invention, thereby preventing an overdose of the pharmacologically active compound (A), particularly due to comminution of the pharmaceutical dosage form by mechanical action. Preferably, the mechanical action is selected from the group consisting of chewing, grinding in a mortar, pounding, and using apparatuses for pulverizing conventional pharmaceutical dosage forms.

The invention is explained below with reference to examples. These explanations are given merely by way of example and do not limit the general concept and scope of the invention.

#### Example 1:

Oblong shaped extrusion dies with the measurements 5\*15 mm and 7\*18 mm were investigated.

A powder blend was prepared. The composition is given in the table here below:

Example 1 per tablet [mg]	Excipient	[%]
174.72	Tapentadol HCL	38.83
166.83	Polyethylenoxide 7000000	37.07
63.00	Hypromellose 100000 mPa*s	14.00
45.00	Macrogol 6000	10.00
0.45	$\alpha$ -Tocopherol	0.10
450.00		

The powder blend was the basis for the following sub-examples:

Sub-Example	Description
1-1	Extrudate 6 mm round die
1-2	Extrudate 5x15 mm oblong-shaped die
1-3	Tablets 7x17 mm oblong from extrudate „round“
1-4	Tablets 7x17 mm H9-shaped from extrudate „round“
1-5	Tablets 7x17 mm oblong from extrudate „oblong“
1-6	Tablets 7x17 mm H9-shaped from extrudate „oblong“

The investigated sub-examples allow for a comparison of the extrusion die's influence on the tablet properties.

#### Example 2:

A powder blend was prepared. The composition is given in the table here below:

Example 2 per tablet [mg]	Excipient	[%]
291.2	Tapentadol HCL	41.6
245.0	Polyethylenoxide 7000000	35.0
98.0	Hypromellose 100000 mPa*s	14.0
65.1	Macrogol 6000	9.3
0.7	$\alpha$ -Tocopherol	0.1
700.0		

The powder blend was the basis for the following sub-examples:

Sub-Example	Description
2-1	Extrudate 7 mm round die
2-2	Extrudate 7x18 mm oblong-shaped die
2-3	Tablets 9x21 mm oblong from extrudate „round“
2-4	Tablets 9x21 mm H0-shaped from extrudate „round“
2-5	Tablets 8.6x22.6 mm H1-shaped from extrudate „round“
2-6	Tablets 9x21 mm oblong from extrudate „oblong“
2-7	Tablets 9x21 mm H0-shaped from extrudate „oblong“
2-8	Tablets 8.6x22.6 mm H1-shaped from extrudate „oblong“

The investigated sub-examples allow for a comparison of the extrusion die's influence on the tablet properties.



### *Methods of Manufacture*

#### a) Extrusion

Extrusion was performed on a Leistritz® PH27micro twin-screw extruder with the throughput reduced to 3.5 kg/h. The temperatures of the individual heating zones were adjusted to values from 30 °C to 135 °C.

#### b) Cutting

Cutting was done using a Schlicht® CC250 cutting machine for the round extrudates and by hand using a bread slicer for the oblong-shaped extrudates. Manual cutting led to a highly inferior quality of the extrudates including, but not limited to, much more surface defects.

#### Tablet Forming

Tablet forming was conducted on a Korsch® EK0 for the 7\*17 mm H9 format. All other tablets were shaped on a Kilian® S250.

### *Analytical Methods*

#### a) Dimensions

Dimensions were measured using a manual caliber.

#### b) Resistance to Crushing

Resistance to crushing was measured on a Sotax® HT100 with plain brackets. Tablet orientation was lengthwise.

#### c) Dissolution

Dissolution measurement was conducted according to Ph Eur. 2.9.3 in a paddle apparatus with sinker, rotation speed 50 rpm at 37 °C in simulated intestinal fluid (900 ml, pH 6.6, KH<sub>2</sub>PO<sub>4</sub> + NaOH). 6 Measurements were made for each sample (n=6). Release was monitored by UV spectroscopy at 271 nm.

### *Results*

#### a) Extrusion - Example 1

The extrusion was possible without any unexpected issues. As exactly identical extruder settings were used, a remarkable observation can be made.

Extrusion die	6 mm (round)	5x15 mm (oblong)
Melt temperature [°C]	119	91

Power consumption [%]	68	68
Melt pressure [bar]	79	75

The above data shows the melt temperature of the extrudate gone through the round die to be significantly higher than that of the extrudate produced with the oblong-shaped die. As the strands' appearances were visually identical the use of the oblong-shaped leads to a lower melt temperature and is therefore less demanding for the material. The back pressure was observed to be minimal lower for the oblong-shaped die than for the round one.

#### a) Extrusion - Example 2

The extrusion was possible without any unexpected issues. As exactly identical extruder settings were used, a remarkable observation can be made.

Extrusion die	7mm (round)	7x18mm (oblong)
Melt temperature [°C]	128	90
Power consumption [%]	67	67
Melt pressure [bar]	74	59

The above data shows again shows the melt temperature of the extrudate gone through the round die to be significantly higher than that of the extrudate produced with the oblong-shaped die. As the strands' appearances were visually identical the use of the oblong-shaped leads to a lower melt temperature and is therefore less demanding for the material. The back pressure was observed to be about 20 % lower for the oblong-shaped die than for the round one.

#### b) Tablet Forming: Dimensions, Appearance, and Resistance to Crushing

##### *Oblong biconvex tablets:*

Example 1	1-3	1-5
Extrusion Die	6 mm round	5*15 mm oblong
Appearance (% with navel, n=50)	22	0
Length [mm] (mean, min.-max., n=10)	16.28 (16.22 – 16.35)	16.76 (16.73 – 16.81)
Width [mm] (mean, min.-max., n=10)	6.99 (6.98 – 7.00)	6.94 (6.91 – 6.95)
Thickness [mm] (mean, min.-max., n=10)	4.82 (4.79 – 4.84)	4.73 (4.66 – 4.95)
Resistance to Crushing [N] (mean, n=50), range given in parenthesis	931 (474 – >1000)	978 ( 405 – >1000)

As the resistance to crushing test is performed at the upper end of the range of the apparatus, the mean value is only informative.

The results show a superiority of sub-example 1-5 over 1-3. In the latter 22% of the tablets showed a navel against the total absence of navels in the first. This finding hints for a better forming of the tablets and is supported by the length measurement: 1-5 forms out the punch more completely which results in significantly longer tablets. Resistance to crushing is slightly higher for 1-5. The deformed tablets of both batches are of similar appearance.

*Oblong, H-shaped tablets:*

Example 1	1-4	1-6
Extrusion Die	6 mm round	5*15 mm oblong
Appearance (% with navel, n=50)	0 (n=46)	0 (n=43)
Length [mm] (mean, min.-max., n=10)	16.53 (16.52 – 16.55)	16.85 (16.80 – 16.89)
Width [mm] (mean, min.-max., n=10)	7.04 (7.03 – 7.04)	6.99 (6.99 – 7.00)
Thickness [mm] (mean, min.-max., n=10)	4.13 (4.05 – 4.18)	4.01 (3.91 – 4.12)
Resistance to Crushing [N] (mean, n=50), range given in parenthesis	542 (249 – >1000)	510 (294 – >1000)

As the resistance to crushing test is performed at the upper end of the range of the apparatus, the mean value is only informative.

The results presented in the above table show a superiority of sub-example 1-6 over 1-4. Although there are no navelled tablets in both batches sub-example 1-6 forms out more accurately. This is again a conclusion from the length measurement: 1-6 forms out the punch more completely which results in significantly longer tablets. Even if a superiority in the resistance to crushing cannot be shown, the picture of the tablets taken after this test hints for an advantage of sub-example 1-6. While most tablets of 1-4 show a characteristic hole in the trough section which results from the previously noted tearing apart of the H-shape, only a single tablet of 1-6 show a hole, but outside the trough area. This finding indicates an increased inherent strength of sub-example 1-6.

*Oblong biconvex tablets:*

Example 2	2-3	2-6
Extrusion Die	7 mm round	7*18 mm oblong
Appearance (% with navel, n=50)	0	6
Length [mm] (mean, min.-max., n=10)	20.26 (20.24 – 20.27)	20.67 (20.57 – 20.84)
Width [mm] (mean, min.-max., n=10)	9.00 (8.98 – 9.03)	8.95 (8.91 – 9.01)
Thickness [mm] (mean, min.-max., n=10)	5.38 (5.36 – 5.42)	5.31 (5.13 – 5.46)
Resistance to Crushing [N] (mean, n=50), range given in parenthesis	1000 (998 – >1000)	942 (483 – >1000) (n=49)

As the resistance to crushing test is performed at the upper end of the range of the apparatus, the mean value is only informative.

The above data indicates sub-example 2-6 to have more navels. This could be an artifact of the manual cutting and should not be overrated. The length measurement again shows the oblong-shaped extrudate to fill the punch more completely, as previously mentioned.

Resistance to crushing is quite similar but values below about 1000N are only measured for sub-example 2-6 and can possibly be linked to the appearance defects. The appearance of the tablets after the test is quite similar.

*Oblong, H-shaped tablets:*

Example 2	2-4	2-7
Extrusion Die	7 mm round	7*18 mm oblong
Appearance (% with navel, n=50)	2	34
Length [mm] (mean, min.-max., n=10)	20.33 (20.29 – 20.38)	20.68 (20.52 – 20.84)
Width [mm] (mean, min.-max., n=10)	9.01 (8.99 – 9.02)	8.99 ( 8.96 – 9.02)
Thickness [mm] (mean, min.-max., n=10)	4.32 (4.29 – 4.34)	4.30 (4.21 – 4.39)
Resistance to Crushing [N] (mean, n=50), range given in parenthesis	292 (211 – 444) (n=47)	479 (267 – >1000)

As the resistance to crushing test is performed at the upper end of the range of the apparatus, the mean value is only informative.

As can be seen from the above table, sub-example 2-7 has more optical defects and again the oblong-shaped extrudate fill the tableting punch more completely. Resistance to crushing is about 60 % higher than that of the tablets from the round extrudate. The photograph of the tablets after the test shows again an advantage for the oblong-shaped extrudate.

*Oblong, H-shaped tablets:*

Example 2	2-5	2-8
Extrusion Die	7 mm round	7*18 mm oblong

Appearance (% with navel, n=50)	44	52
Length [mm] (mean, min.-max., n=10)	21.79 (21.70 – 21.87)	22.04 (21.97 – 22.12)
Width [mm] (mean, min.-max., n=10)	8.62 (8.60 – 8.65)	8.61 (8.60 – 8.61)
Thickness [mm] (mean, min.-max., n=10)	4.23 (4.20 – 4.25)	4.24 (4.13 – 4.34)
Resistance to Crushing [N] (mean, n=50), range given in parenthesis	353 (215 – >1000)	550 (249 – >1000)

As the resistance to crushing test is performed at the upper end of the range of the apparatus, the mean value is only informative.

There are practically no qualitative differences between tablets that are H0-shaped and those that are H1-shaped. The amount of tablets showing a navel is more similar between sub-examples 2-5 and 2-8 than it has been before. This however should not be overrated due to the less accurate quality of the manually cut extrudates.

The results of in vitro dissolution experiments are displayed in Figures 6 to 10.

Figure 6: Dissolution profile of example 1 shaped to a 7\*17 mm oblong tablet, mean, n=3

Figure 7: Dissolution profile of example 1 shaped to a 7\*17 mm H9-shaped tablet, mean, n=3

Figure 8: Dissolution profile of example 2 shaped to a 9\*21 mm oblong tablet, mean, n=3

Figure 9: Dissolution profile of example 2 shaped to a 9\*21 mm H0-shaped tablet, mean, n=3

Figure 10: Dissolution profile of example 2 shaped to a 8.6\*22.6 mm H1-shaped tablet, mean, n=3

The dissolution profiles of all produced tablets show an acceleration of the oblong tablet formed from the oblong-shaped extrudate compared to the oblong tablet formed from the cylindrical extrudate, irrespective from the tablet's format.

The extent of this dissolution acceleration is illustrated by Figures 11 and 12. By using an oblong shaped extrusion die acceleration in dissolution for the non H-shaped oblong tablet is

achieved that is equivalent to that of the use of an H-shaped tablet punch made from an extrudate made with a cylindrical die.

Figure 11: Dissolution for example 1: comparison of H9 format from round extrudate to oblong format from oblong extrudate, mean, n=3

Figure 12: Dissolution for example 2: comparison of H0 format from round extrudate to oblong format from oblong extrudate, mean, n=3

It becomes evident from the dissolution data that dissolution speeds up for oblong tablets formed from oblong-shaped extrudates in comparison to that derived from cylindrical extrudates. This acceleration has an extent that apparently makes it possible to achieve sufficiently fast dissolution with (conventional) biconvex oblong tablets, i.e. as far as the dissolution rate is concerned, there is no need to provide the oblong tablets in H-shaped format.

This finding is unexpected and indicates some structural changes within the extrudate in dependency from the extrusion die chosen or hints for an un-isometric behavior of the extrudate as such.

Further, extrusion through oblong-shaped dies is advantageous if the extrudate is to be formed to an oblong-shaped tablet. Rupture during the resistance to crushing test does not occur at the desired breaking forces. Optical defects ("navel") might be reduced or even completely eliminated. The deviating dissolution behavior hints for some structural changes in the extrudate.

### Example 3:

A powder blend was prepared. The composition is given in the table here below:

Example 3 per tablet [mg]	Excipient	[%]
40.0	Tramadol HCL	18.60
122.1	Polyethylenoxide 7000000	56.80
21.5	Hypromellose 100000 mPa*s	10.00
29.2	Macrogol 6000	13.56
0.4	$\alpha$ -Tocopherol	0.20
1.8	Citric acid anhydrous	0.84
215.0		

The powder blend was the basis for the following sub-examples:

Sub-Example	Description
3-1	oblong slices
3-2	oblong slices, folded twice, then tabletted

In analogy to example 2, extrusion was performed using a 7x18mm oblong-shaped die. In sub-example 3-1 the crude extruded slice was investigated without further modification. In sub-example 3-2 the crude extruded slice was folded twice and thereafter, press-formed into tablets with 9 mm diameter and a radius of curvature of 7.2 mm.

The release profile for tramadol HCl was measured in analogy to example 2. The results are shown in Figure 13.

Patent claims:

1. A hot-melt extruded pharmaceutical dosage form with controlled release of a pharmacologically active ingredient (A) embedded in a matrix comprising a polymer (C), the dosage form having an oblong shape comprising a longitudinal direction of extension, a transversal direction of extension orthogonal to the longitudinal direction of extension, a front side, an opposite back side and a circumferential rim between said front and back side;  
  
wherein
  - the core of the pharmaceutical dosage form has a morphological orientation caused by hot-melt extrusion that is substantially orthogonal to the longitudinal direction of extension of the dosage form; and/or
  - the release per area of the pharmacologically active ingredient (A) through the front side and the opposite back side is faster than the release through the circumferential rim.
2. The dosage form according to claim 1, wherein the morphological orientation caused by hot-melt extrusion is substantially orthogonal to the transversal direction of extension of the dosage form.
3. The dosage form according to claim 1 or 2, which comprises a monolithic core.
4. The dosage form according to any of the preceding claims, wherein the pharmacologically active ingredient (A) is an opioid.
5. The dosage form according to any of the preceding claims, wherein polymer (C) is a polyalkylene oxide having a weight average molecular weight of at least 200,000 g/mol.
6. The dosage form according to any of the preceding claims, wherein the content of polymer (C) is at least 30 wt.-%, based on the total weight of the dosage form.
7. The dosage form according to any of the preceding claims, wherein the relative length ratio of the longitudinal direction of extension to the transversal direction of extension is at least 1.1 : 1.
8. The dosage form according to any of the preceding claims, which comprises a film coating.



9. The dosage form according to any of the preceding claims, which releases the pharmacologically active ingredient (A) under *in vitro* conditions in artificial gastric juice according to the following release profile:
- after 0.5 h at least 5 wt.-%,
  - after 1 h at least 10 wt.-%,
  - after 3 h at least 20 wt.-%,
  - after 6 h at least 35 wt.-%, and
  - after 12 h at least 55 wt.-%,
- based on the total weight of the pharmacologically active ingredient (A) initially contained in the dosage form.
10. A process for the manufacture of a hot-melt extruded pharmaceutical dosage form with controlled release of a pharmacologically active ingredient (A) embedded in a matrix comprising a polymer (C), the dosage form exhibiting a breaking strength of at least 300 N and having an oblong shape comprising a longitudinal direction of extension, a transversal direction of extension orthogonal to the longitudinal direction of extension, a front side, an opposite back side and a circumferential rim between said front and back side, comprising the steps of
- (a) hot-melt extruding a mass comprising
    - the pharmacologically active ingredient (A) and
    - the polymer (C),through an oblong die thereby obtaining an extrudate with an oblong cross-section;
  - (b) cutting said extrudate into slices having two opposing cut surfaces of oblong shape;
  - (c) placing said slices into a tableting tool comprising upper punch and lower punch in a manner so that the opposing surfaces of oblong shape face said upper and lower punch, respectively;
  - (d) press-forming dosage forms from the slices; and
  - (e) optionally, applying a film coating.
11. The process according to claim 10, which is for the manufacture of a dosage form according to any of claims 1 to 9.
12. The process according to claim 10 or 11, wherein step (a) is performed by means of a twin-screw-extruder.

13. The process according to any of claims 10 to 12, wherein at least 50 % of the total surface of the slices obtained in step (b) is formed by the two opposing cut surfaces.
14. A hot-melt extruded pharmaceutical dosage form obtainable by the process according to any of claims 10 to 13.

Figure 1

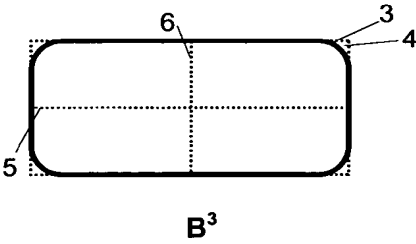
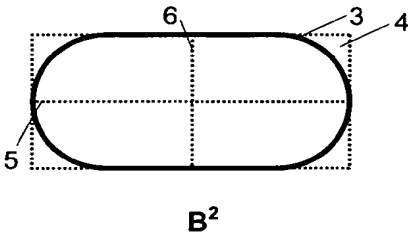
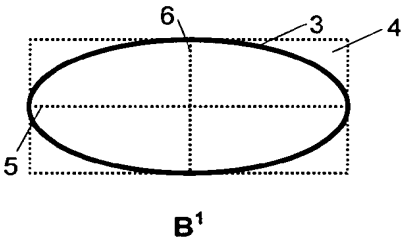
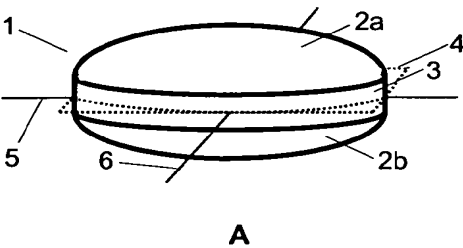
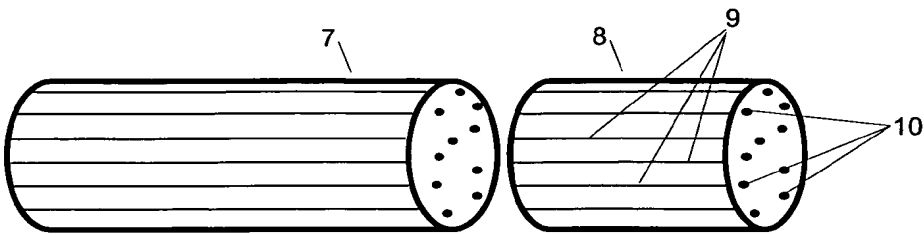
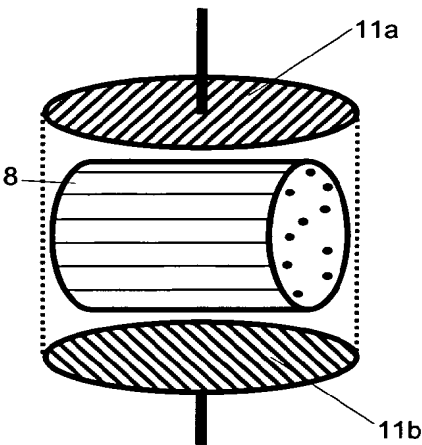


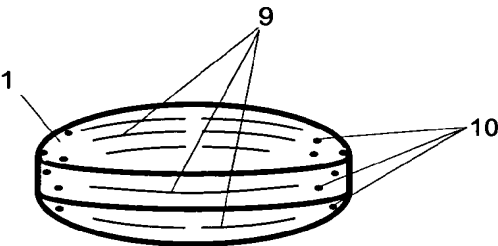
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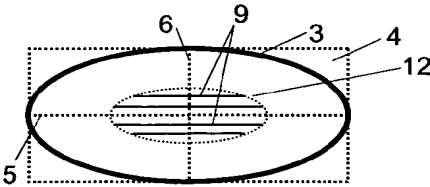
A



B

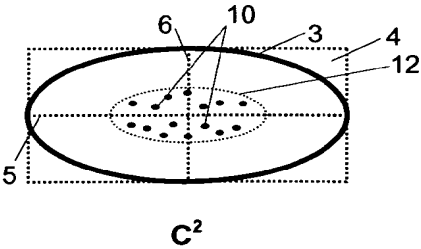
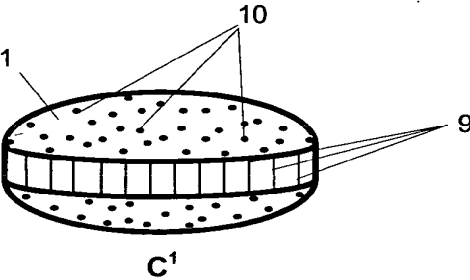
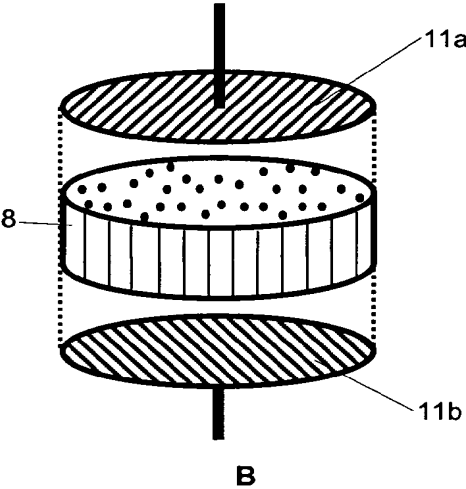
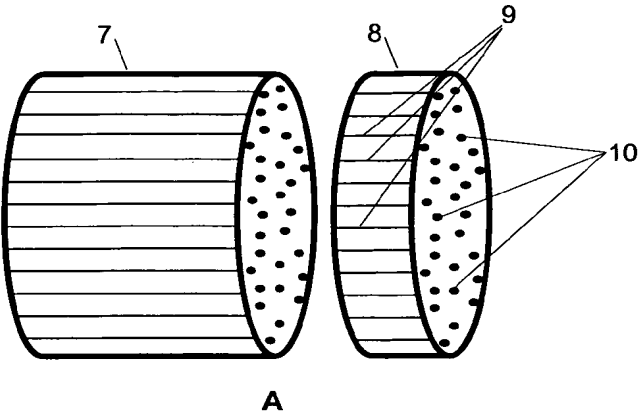


C<sup>1</sup>



C<sup>2</sup>

Figure 3



4/13  
Figure 4

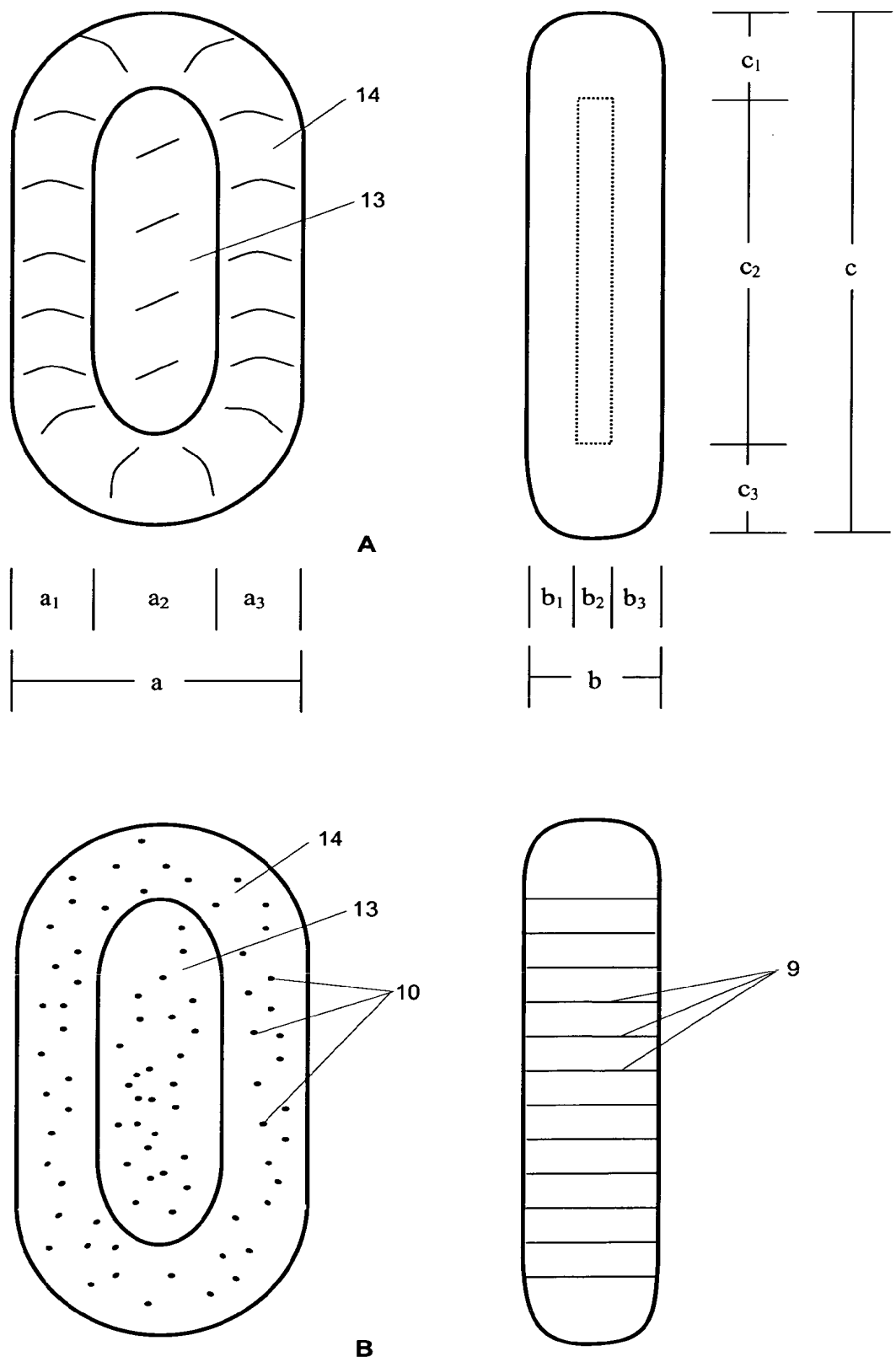


Figure 5

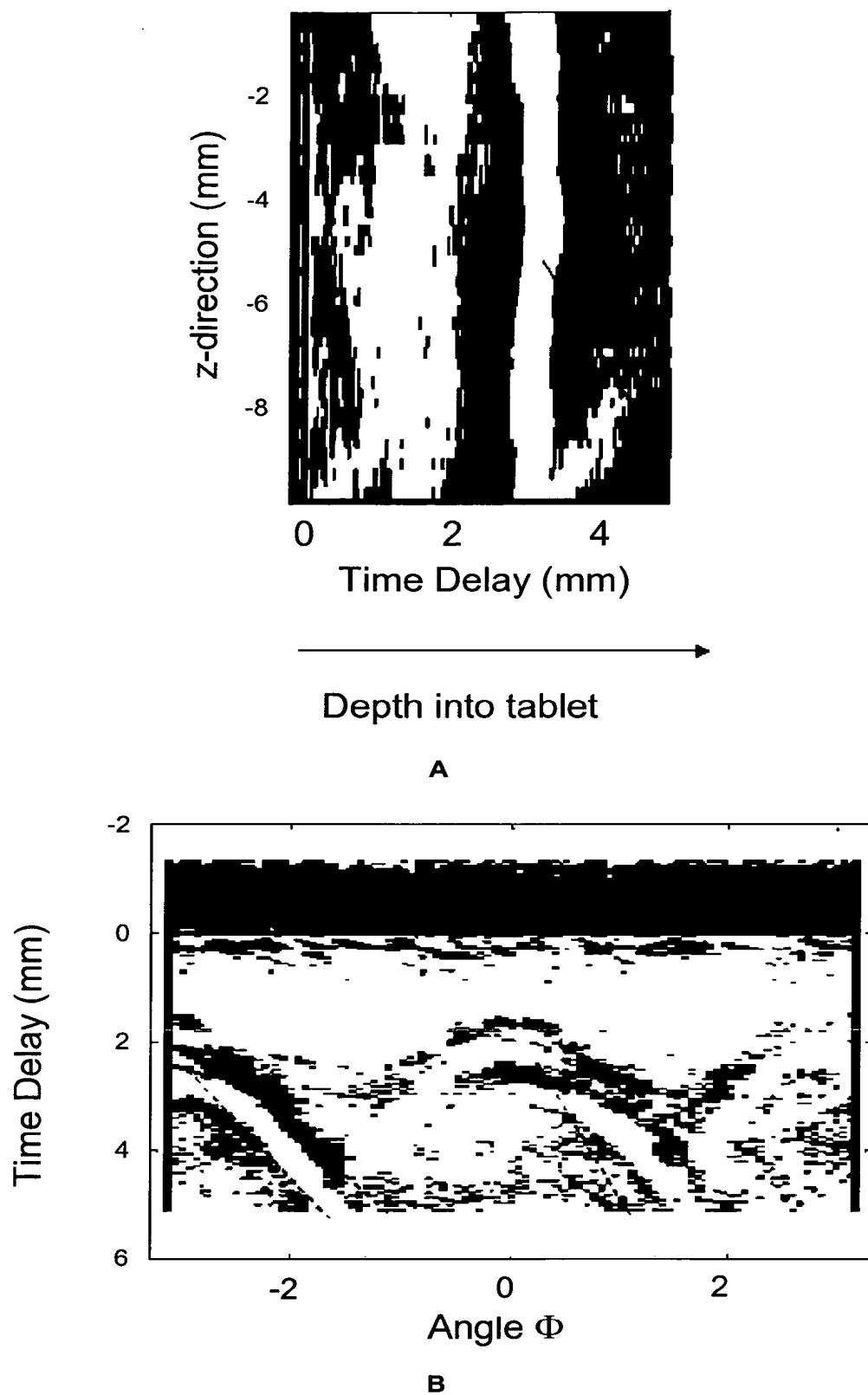


Figure 6

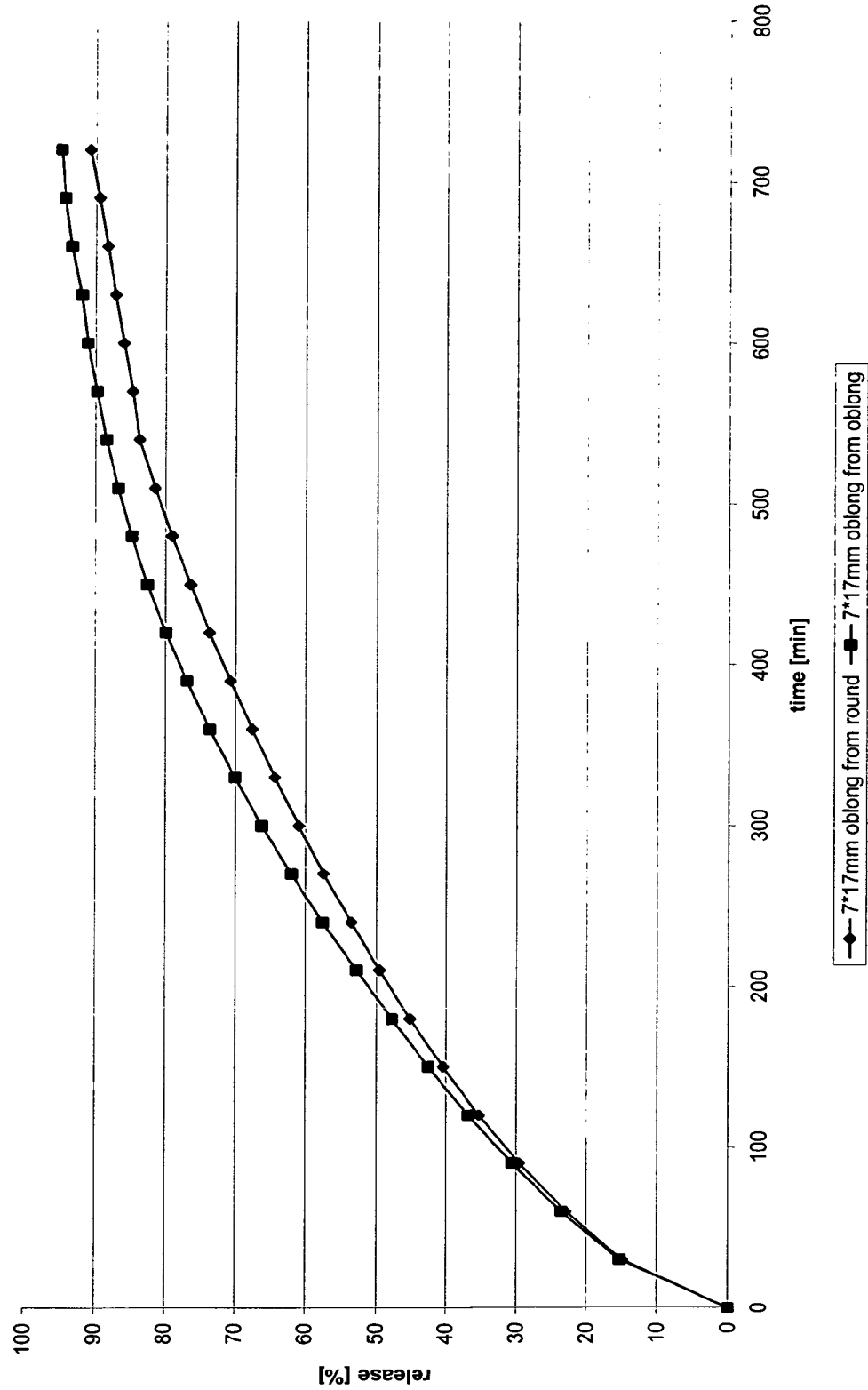




Figure 7

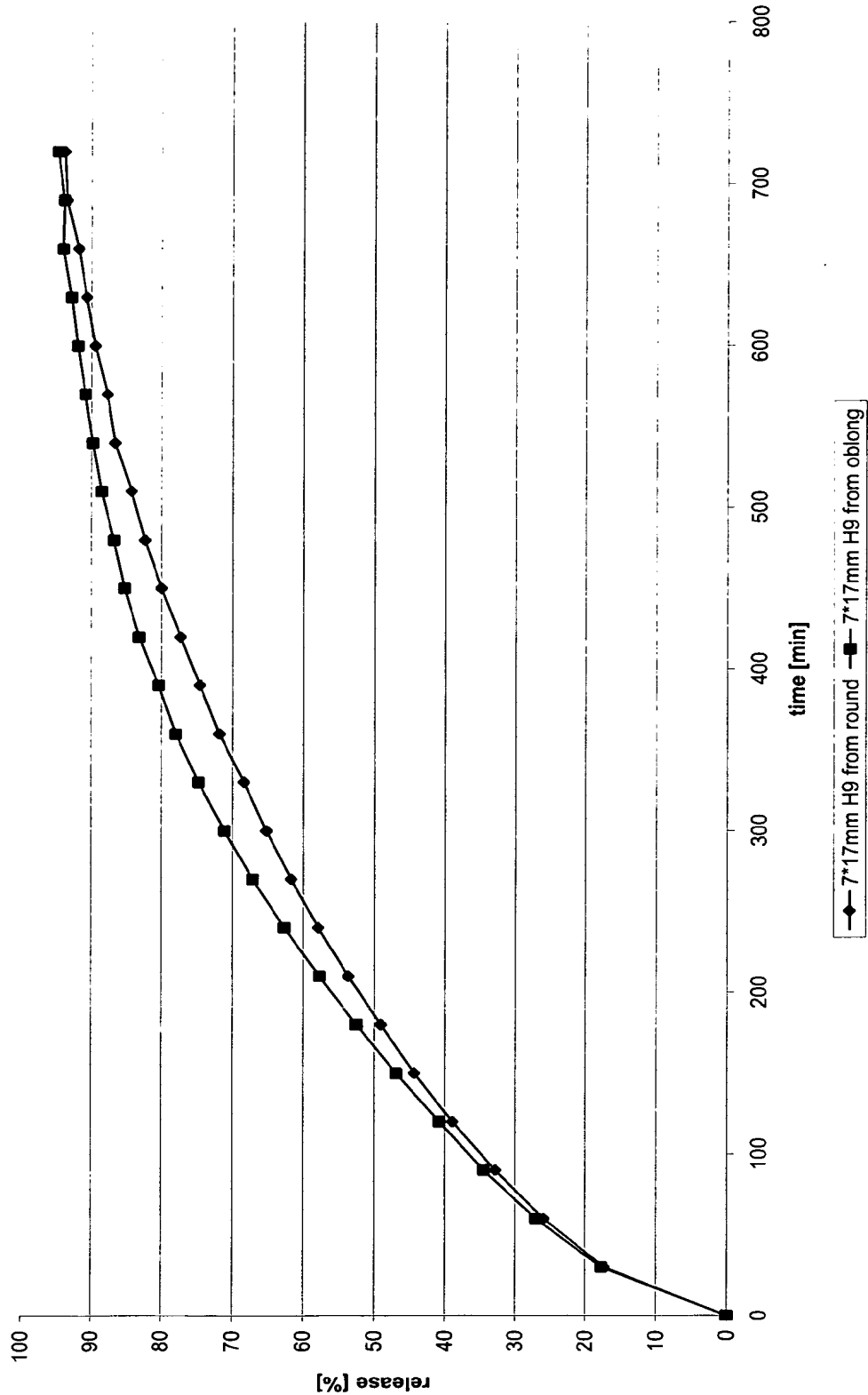


Figure 8

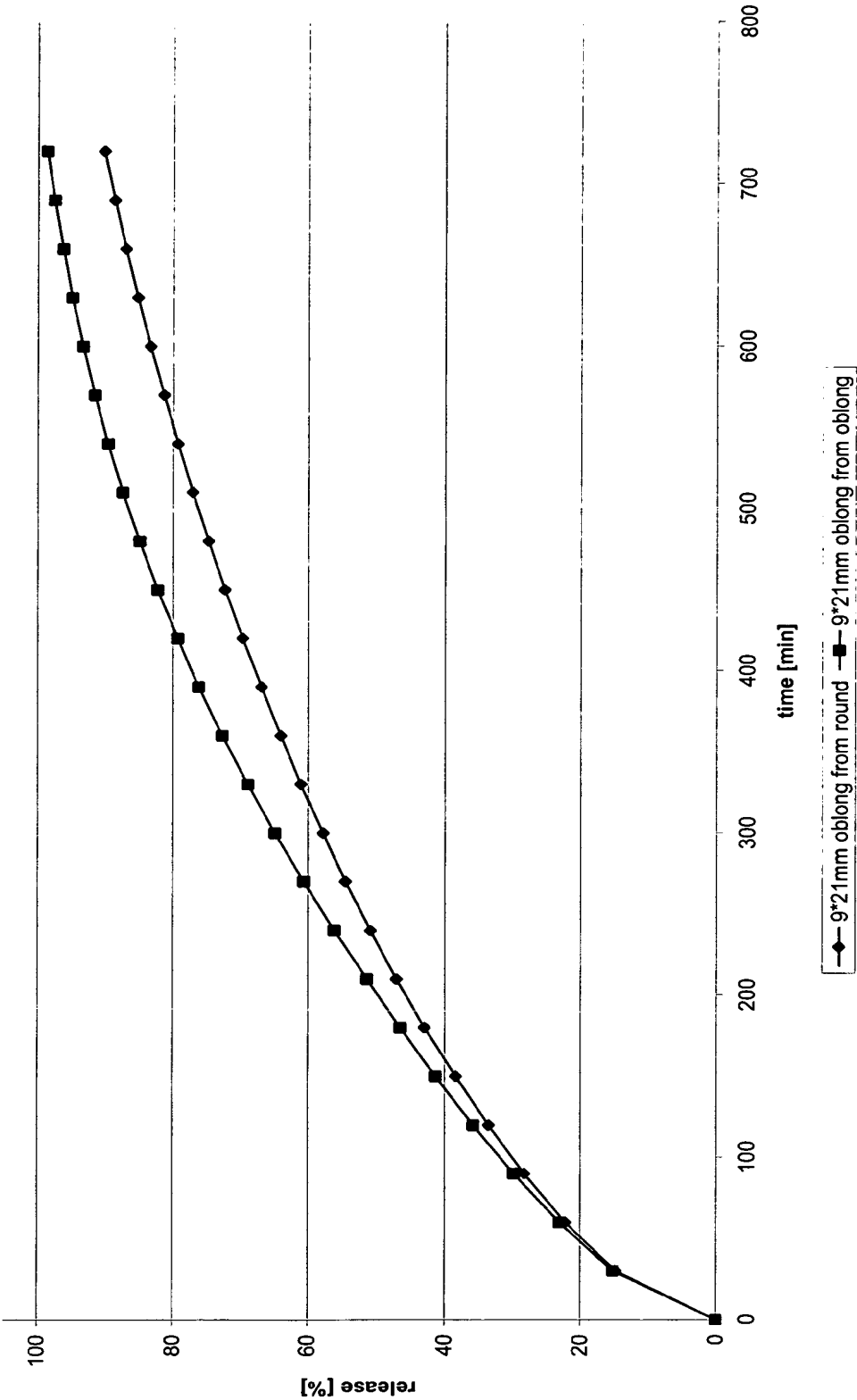


Figure 9

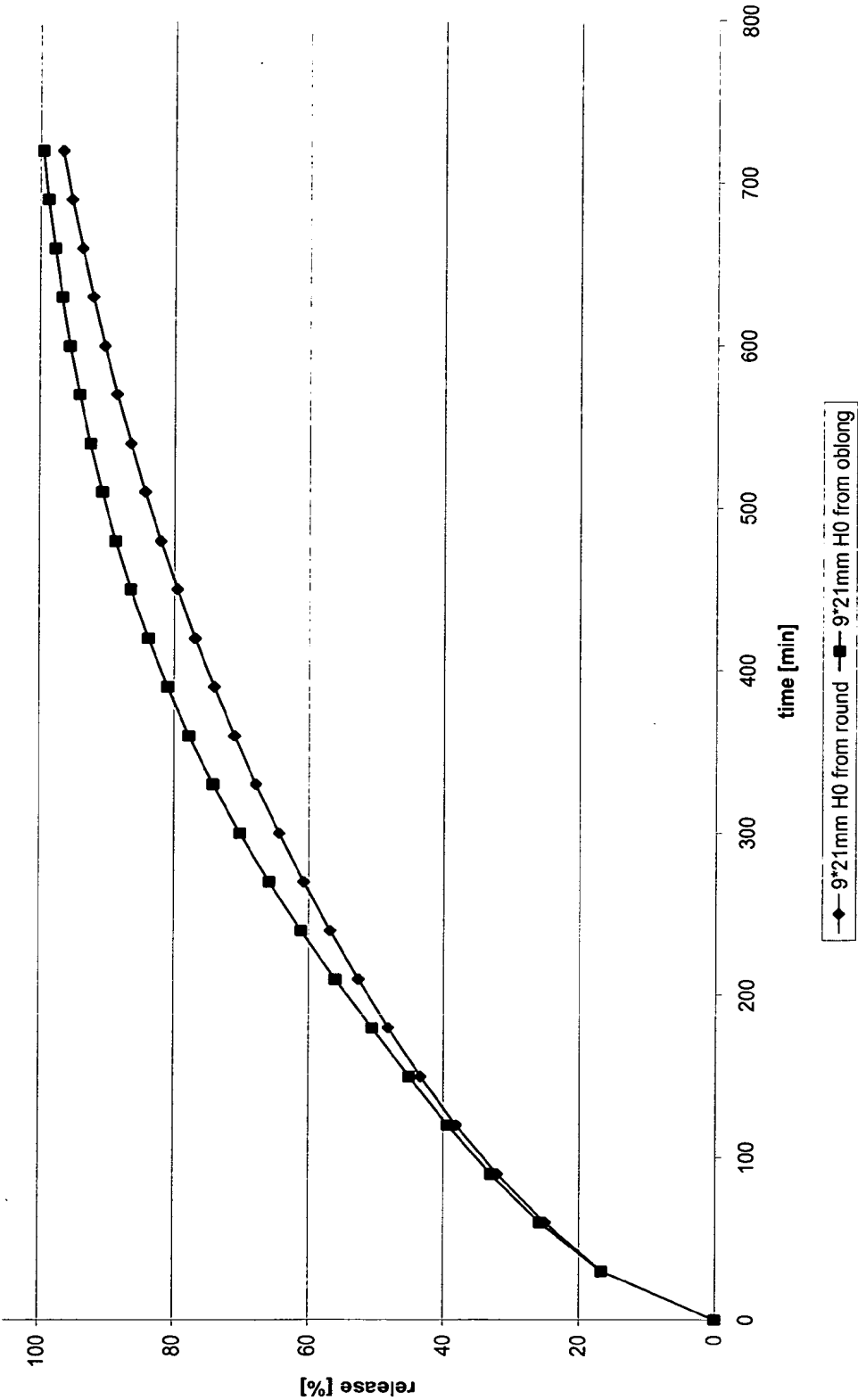


Figure 10

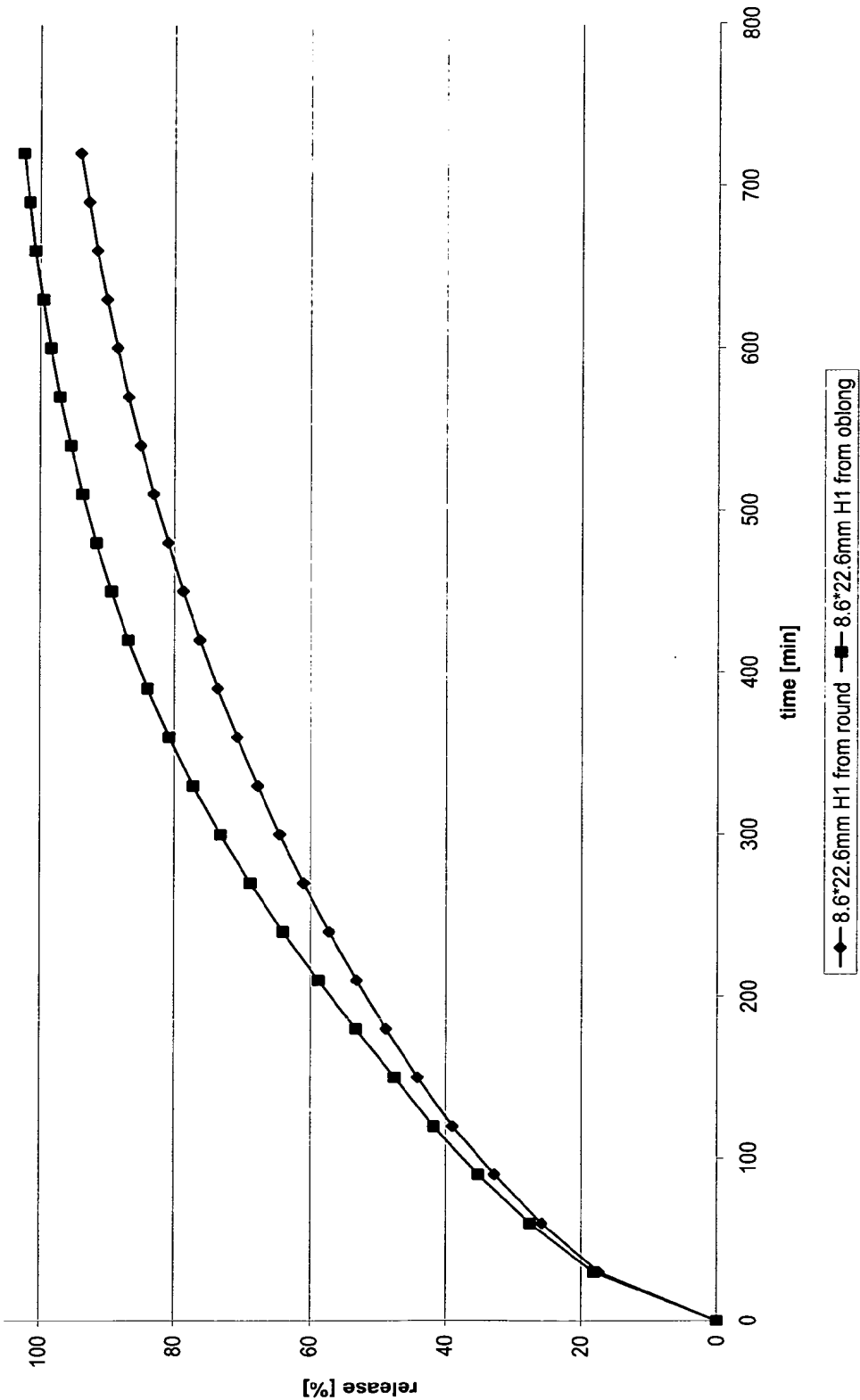


Figure 11

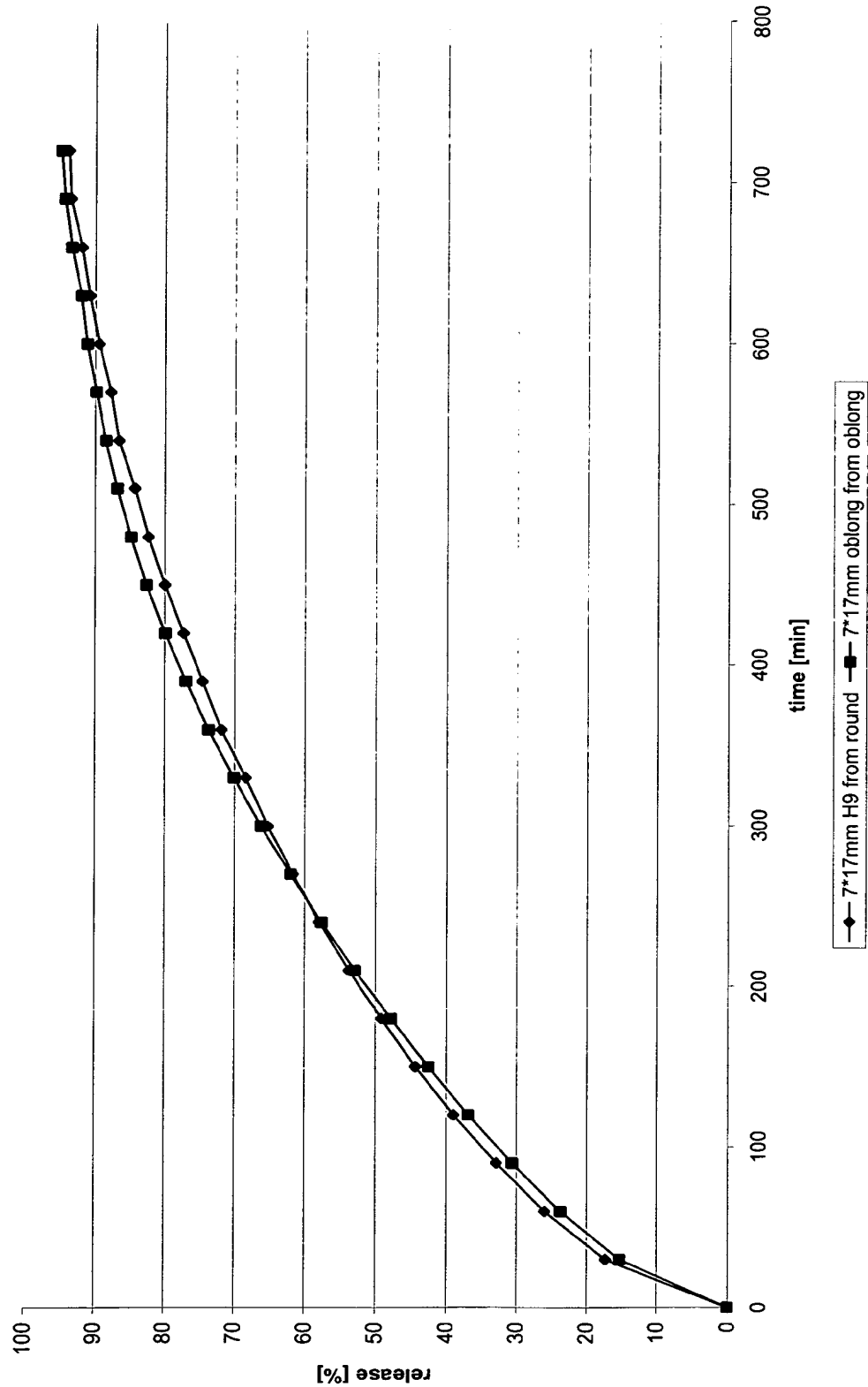


Figure 12

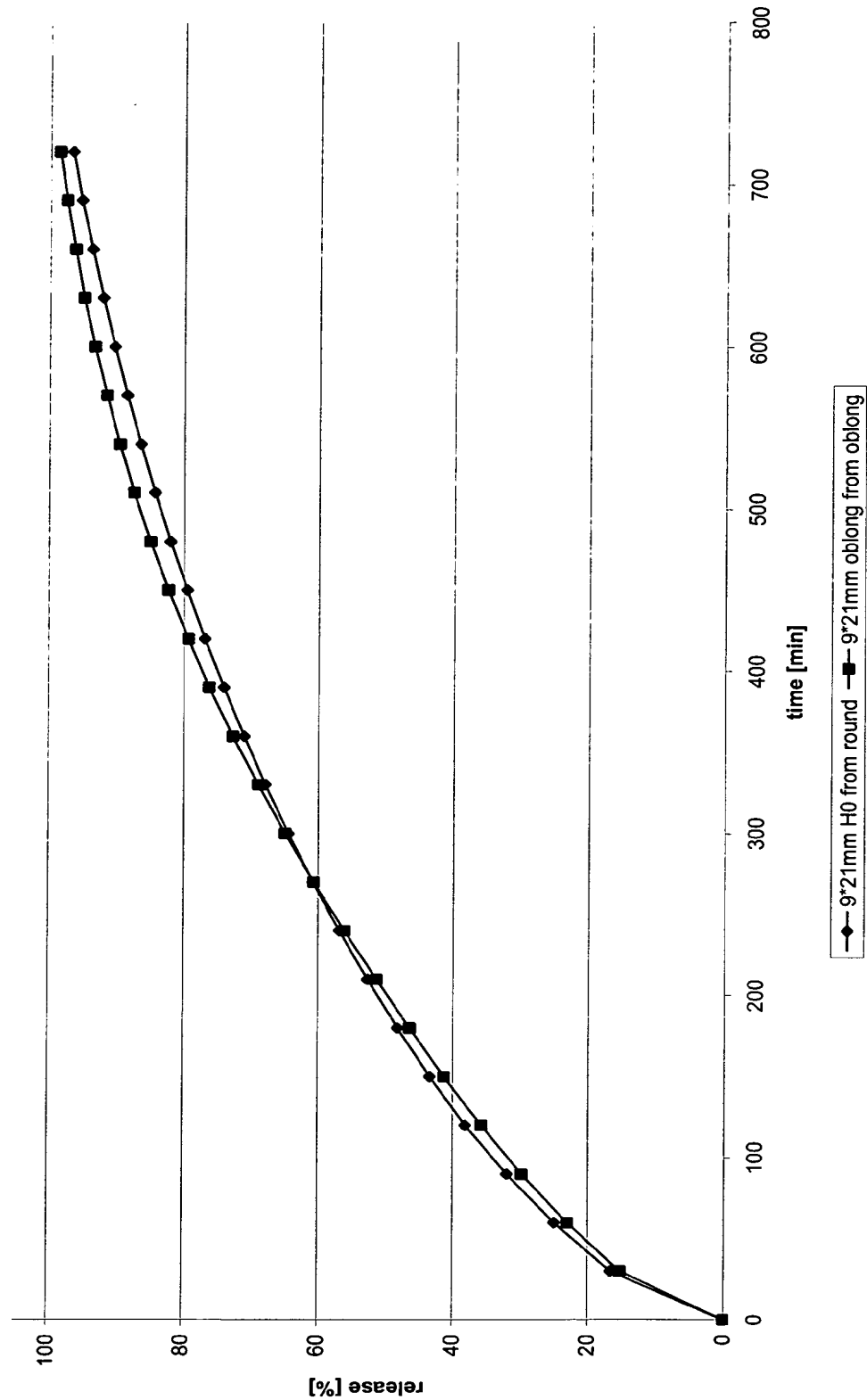
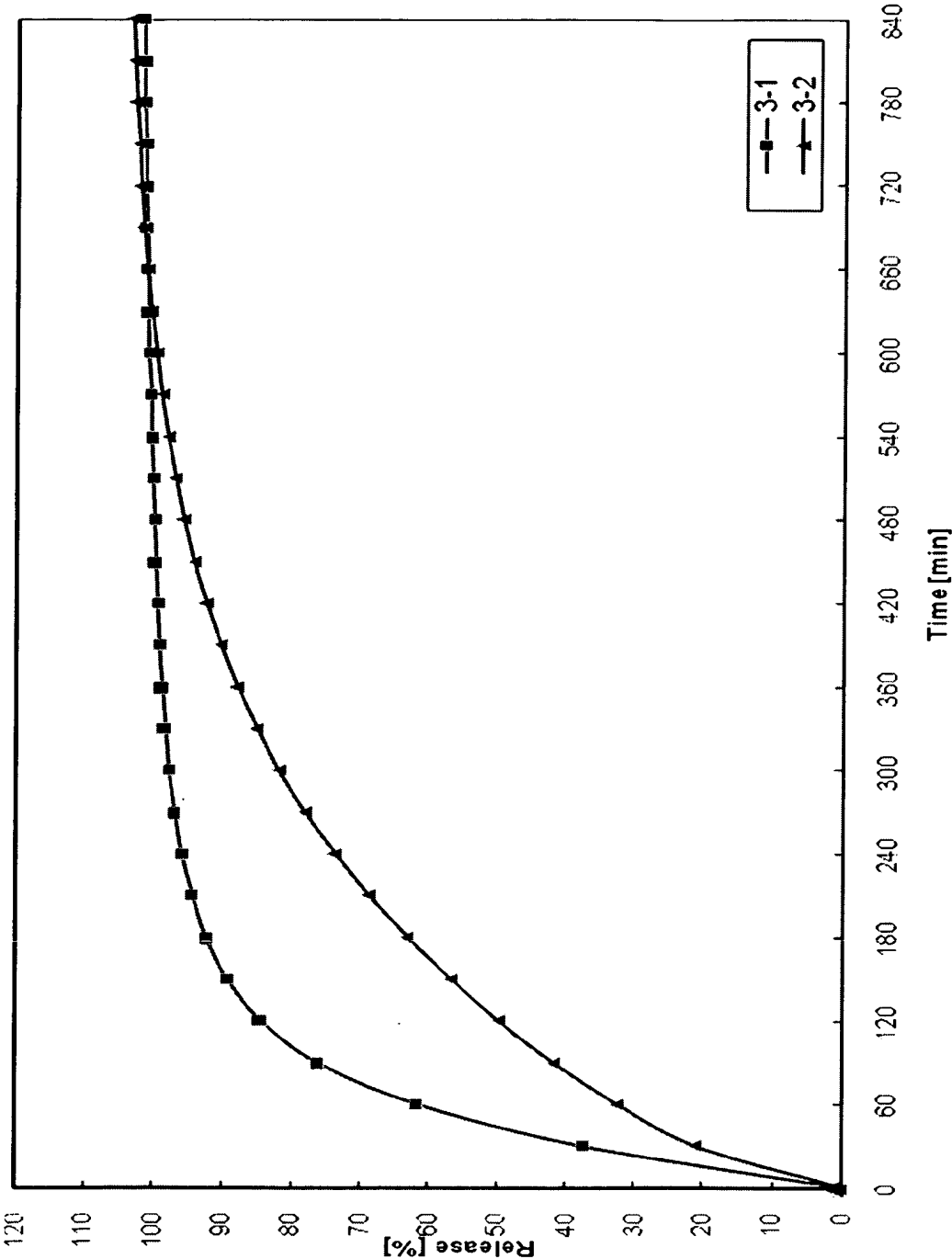


Figure 13



# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2010/004459

## A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K9/20 A61K31/137  
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 10 2005 005446 A1 (GRUENENTHAL GMBH [DE]) 10 August 2006 (2006-08-10) paragraph [0020] - paragraph [0105] claims 1-14 figure 1	1-14
X	DE 44 46 470 A1 (BASF AG [DE]) 27 June 1996 (1996-06-27) paragraph [0013] - paragraph [0048] claims 1-8	1-14
X	WO 2007/103286 A2 (SPHERICS INC [US]; NANGIA AVINASH [US]; JACOB JULES [US]; MOSLEMY PEYM) 13 September 2007 (2007-09-13) claims 1-62	1-14
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

22 November 2010

Date of mailing of the international search report

01/12/2010

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Schifferer, Hermann



## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/004459

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Information on patent family members

International application No

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